

L Number	Hits	Search Text	DB	Time stamp
1	1119	antacid	USPAT; US-PGPUB	2002/08/22 13:32
2	4527	(silicon adj dioxide) and (microcrystalline adj cellulose)	USPAT; US-PGPUB	2002/08/22 13:58
3	134	antacid and ((silicon adj dioxide) and (microcrystalline adj cellulose))	USPAT; US-PGPUB	2002/08/22 13:32
4	18	(antacid and ((silicon adj dioxide) and (microcrystalline adj cellulose))) and simethicone	USPAT; US-PGPUB	2002/08/22 13:43
5	13	((silicon adj dioxide) and (microcrystalline adj cellulose)) and antacid and ((magnesium adj2 silicate) or (magnesium adj aluminosilicate))	USPAT; US-PGPUB	2002/08/22 13:49
6	17	((silicon adj dioxide) and (microcrystalline adj cellulose)) and simethicone and ((magnesium adj2 silicate) or (magnesium adj aluminosilicate))	USPAT; US-PGPUB	2002/08/22 13:49
7	26	prosolv or (silicified adj microcrystalline adj cellulose)	USPAT; US-PGPUB	2002/08/22 14:03
8	2	(prosolv or (silicified adj microcrystalline adj cellulose)) and naproxen	USPAT; US-PGPUB	2002/08/22 14:00
9	2	(bisacodyl or dulcolax or famotidine or prucalopride or diphenoxylate or loperamide or mesalamine or asacol or lactase) and (prosolv or (silicified adj microcrystalline adj cellulose))	USPAT; US-PGPUB	2002/08/22 14:05
10	5	(acetaminophen or ibuprofen or naproxen or ketoprofen or cyclobenzaprine or meloxicam or rofecoxib or celecoxib) and (prosolv or (silicified adj microcrystalline adj cellulose))	USPAT; US-PGPUB	2002/08/22 14:06
-	12651	(magnesium adj2 silicate) or (mgal2si2o8) or angast or (magnesium adj sluminosilicate) or neusilin	USPAT; US-PGPUB	2002/08/22 12:15
-	908	prosolv or (silicified adj microcrystalline adj cellulose) or (cellulose adj2 silica)	USPAT; US-PGPUB	2002/08/22 13:58
-	625	simethicone or mylicon or aligest or simitcone	USPAT; US-PGPUB	2002/08/22 12:16
-	2320	bisacodyl or dulcolax or famotidine or prucalopride or diphenoxylate or loperamide or mesalamine or asacol or lactase	USPAT; US-PGPUB	2002/08/22 14:04
-	0	(simethicone or mylicon or aligest or simitcone) and (bisacodyl or dulcolax or famotidine or prucalopride or diphenoxylate or loperamide or mesalamine or asacol or lactase) and ((magnesium adj2 silicate) or (mgal2si2o8) or angast or (magnesium adj sluminosilicate) or neusilin) and (prosolv or (silicified adj microcrystalline adj cellulose) or (cellulose adj2 silica)))	USPAT; US-PGPUB	2002/08/22 12:18
-	32	((magnesium adj2 silicate) or (mgal2si2o8) or angast or (magnesium adj sluminosilicate) or neusilin) and (prosolv or (silicified adj microcrystalline adj cellulose) or (cellulose adj2 silica))	USPAT; US-PGPUB	2002/08/22 12:18
-	2	((magnesium adj2 silicate) or (mgal2si2o8) or angast or (magnesium adj sluminosilicate) or neusilin) and (prosolv or (silicified adj microcrystalline adj cellulose) or (cellulose adj2 silica))) and (simethicone or mylicon or aligest or simitcone)	USPAT; US-PGPUB	2002/08/22 12:20

-	1	(bisacodyl or dulcolax or famotidine or prucalopride or diphenoxylate or loperamide or mesalamine or asacol or lactase) and (((magnesium adj2 silicate) or (mgal2si2o8) or angast or (magnesium adj sluminosilicate) or neusilin) and (prosolv or (silicified adj microcrystalline adj cellulose) or (cellulose adj2 silica)))	USPAT; US-PGPUB	2002/08/22 12:20
-	1	5458879.pn.	USPAT; US-PGPUB	2002/08/22 13:31

FILE 'HOME' ENTERED AT 09:32:33 ON 22 AUG 2002

=> s neusilin

THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE

Some commands only work in certain files. For example, the EXPAND command can only be used to look at the index in a file which has an index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of commands which can be used in this file.

=> file reg

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

2.31

2.31

FILE 'REGISTRY' ENTERED AT 09:39:15 ON 22 AUG 2002

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

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STRUCTURE FILE UPDATES: 21 AUG 2002 HIGHEST RN 444646-89-3

DICTIONARY FILE UPDATES: 21 AUG 2002 HIGHEST RN 444646-89-3

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNnote 27, Searching Properties in the CAS Registry File, for complete details:

<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=> s neusilin

L1 1 NEUSILIN

=> d

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS

RN 12511-31-8 REGISTRY

CN Silicic acid (H4SiO4), aluminum magnesium salt (2:2:1) (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Aluminosilicic acid (HAlSiO4), magnesium salt (8CI)

CN Magnesium aluminosilicate (MgAl2Si2O8) (6CI, 7CI)

OTHER NAMES:

CN Aluminum magnesium silicate .

CN Angast

CN Magnesium aluminate metasilicate

CN Magnesium aluminosilicate (Mg(AlSiO4)2)

CN Magnesium aluminum silicate (MgAl2(SiO4)2)

CN Magnesium aluminum silicate (MgAl2Si2O8)

CN **Neusilin**

CN **Neusilin FH 2**

CN **Neusilin FL 2**

CN **Neusilin UFL 2**

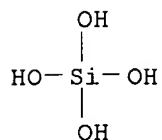
CN **Neusilin US2**

DR 24716-65-2, 50958-44-6, 37303-22-3, 107497-93-8

MF Al . H4 O4 Si . 1/2 Mg

CI COM

LC STN Files: BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CHEMLIST,
CIN, DDFU, DRUGU, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, MRCK*, PROMT,
TOXCENTER, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
CRN (10193-36-9)



Al

1/2 Mg

152 REFERENCES IN FILE CA (1967 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
153 REFERENCES IN FILE CAPLUS (1967 TO DATE)
3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> s prosolv

L2 2 PROSOLV

=> d 1-2

L2 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2002 ACS
RN 212693-81-7 REGISTRY
CN Cellulose, mixt. with silica (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **ProSolv**
CN **ProSolv 90**
CN **ProSolv SMCC 50**
CN **ProSolv SMCC 90**
MF O2 Si . Unspecified
CI MXS
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 7631-86-9

CMF 02 Si

O=Si=O

18 REFERENCES IN FILE CA (1967 TO DATE)
18 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L2 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2002 ACS

RN 9004-34-6 REGISTRY

CN Cellulose (8CI, 9CI) (CA INDEX NAME)

OTHER NAMES:

CN .alpha.-Cellulose

CN .beta.-Amylose

CN 3mAQUACEL

CN 402-2B

CN Alicell LV

CN Alpha Cel PB 25

CN Alphafloc

CN Arbocel

CN Arbocel B 00

CN Arbocel B 600

CN Arbocel B 600/30

CN Arbocel B 800

CN Arbocel B 820C

CN Arbocel BC 1000

CN Arbocel BC 200

CN Arbocel BE 600

CN Arbocel BE 600/10

CN Arbocel BE 600/20

CN Arbocel BE 600/30

CN Arbocel BEM

CN Arbocel BFC 200

CN Arbocel BW 40

CN Arbocel DC 1000

CN Arbocel FD 00

CN Arbocel FD 600/30

CN Arbocel FIC 200

CN Arbocel FT 40

CN Arbocel FT 600/30H

CN Arbocel TF 30HG

CN Arbocel TP 40

CN Avicel

CN Avicel 101

CN Avicel 102

CN Avicel 2330

CN Avicel 2331

CN Avicel 955

CN Avicel CL 611

CN Avicel E 200

CN Avicel F 20

CN Avicel FD 100

CN Avicel FD 101

CN Avicel FD-F 20

CN Avicel M 06

CN Avicel M 15

CN Avicel M 25

CN Avicel NT 020

CN Avicel PH 101

CN Avicel PH 102

CN Avicel PH 105

L1 ANSWER 16 OF 16 REGISTRY COPYRIGHT 2002 ACS

RN 8050-81-5 REGISTRY

CN **Simethicone (8CI, 9CI)** (CA INDEX NAME)

OTHER NAMES:

CN Aligest Plus

CN Antifoam A

CN DC Antifoam A

CN KS 66

CN KS 66 (silicone)

CN Mylicon

CN **Sentry Simethicone GS**

CN Simiticone

DR 9006-05-7, 1646-73-7, 39349-90-1

MF Unspecified

CI COM, MAN

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BIOBUSINESS, BIOSIS,
BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS,
CHEMLIST, CIN, CSCHM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, HSDB*,
IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, PHARMASEARCH,
PROMT, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

189 REFERENCES IN FILE CA (1967 TO DATE)

2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

189 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=>

L7 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2002 ACS
RN 603-50-9 REGISTRY
CN Phenol, 4,4'-(2-pyridinylmethylene)bis-, diacetate (ester) (9CI) (CA
INDEX NAME)

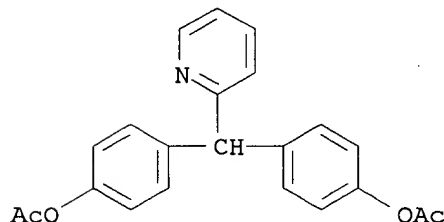
OTHER CA INDEX NAMES:

CN Phenol, 4,4'-(2-pyridylmethylene)di-, diacetate (6CI, 7CI)
CN Phenol, 4,4'-(2-pyridylmethylene)di-, diacetate (ester) (8CI)

OTHER NAMES:

CN 4,4'-(2-Pyridylmethylene)diphenol diacetate
CN Bis(p-acetoxyphenyl)-2-pyridylmethane
CN **Bisacodyl**
CN Brocalax
CN Dulcolan
CN Dulcolax
CN Durolax
CN Fenilaxan
CN Hillcolax
CN Iivilax
CN LA96a
CN Laco
CN Laxadin
CN Laxans
CN Laxine
CN Laxorex
CN Neolax
CN Nigalax
CN Perilax
CN Ppyrilax
CN Sanvacual
CN Telemin
CN Videx
CN Zetrax
MF C22 H19 N O4
CI COM

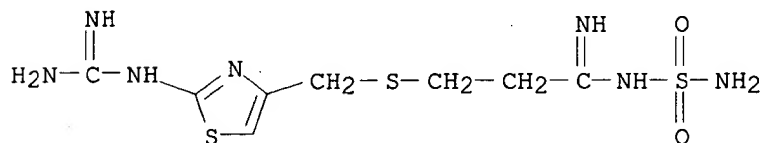
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*,
BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT,
CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU,
EMBASE, HODOC*, HSDB*, IPA, MEDLINE, MRCK*, PHAR, PHARMASEARCH, PROMT,
RTECS*, SPECINFO, TOXCENTER, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

197 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
197 REFERENCES IN FILE CAPLUS (1967 TO DATE)
30 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L9 ANSWER 5 OF 5 REGISTRY COPYRIGHT 2002 ACS
 RN 76824-35-6 REGISTRY
 CN Propanimidamide, 3-[[[2-[(aminoiminomethyl)amino]-4-thiazolyl)methyl]thio]-
 N-(aminosulfonyl)- (9CI) (CA INDEX NAME)
 OTHER NAMES:
 CN 3-[(2-Diaminomethyleneaminothiazol-4-yl)methylthio]-N-
 sulfamoylpropionamide
 CN **Famotidine**
 CN Gaster
 CN MK 208
 CN N-(Aminosulfonyl)-3-[[[2-[(diaminomethylene)amino]-4-
 thiazolyl)methyl]thio]propanimidamide
 CN YM 11170
 FS 3D CONCORD
 MF C8 H15 N7 O2 S3
 CI COM
 LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
 BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST,
 CIN, CSCHEM, DDFU, DIOGENES, DRUGPAT, DRUGU, EMBASE, HSDB*, IFICDB,
 IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PHAR, PHARMASEARCH,
 PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL,
 VETU
 (*File contains numerically searchable property data)
 Other Sources: DSL**, WHO
 (**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1030 REFERENCES IN FILE CA (1967 TO DATE)
 33 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 1032 REFERENCES IN FILE CAPLUS (1967 TO DATE)

N 179474-81-8 REGISTRY

CN 7-Benzofurancarboxamide, 4-amino-5-chloro-2,3-dihydro-N-[1-(3-methoxypropyl)-4-piperidinyl]- (9CI) (CA INDEX NAME)

OTHER NAMES:

CN **Prucalopride**

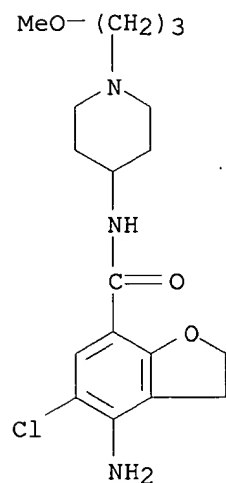
FS 3D CONCORD

MF C18 H26 Cl N3 O3

CI COM

SR CA

LC STN Files: ADISINSIGHT, BIOSIS, BIOTECHNO, CA, CAPLUS, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, PHAR, SYNTHLINE, TOXCENTER, USAN, USPATFULL

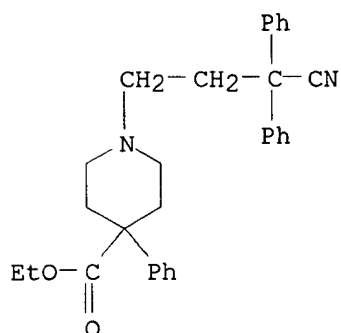


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

23 REFERENCES IN FILE CA (1967 TO DATE)

23 REFERENCES IN FILE CAPLUS (1967 TO DATE)

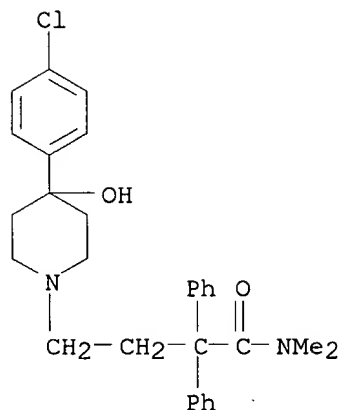
RN .915-30-0 REGISTRY
 CN 4-Piperidinecarboxylic acid, 1-(3-cyano-3,3-diphenylpropyl)-4-phenyl-,
 ethyl ester (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN Isonipectic acid, 1-(3-cyano-3,3-diphenylpropyl)-4-phenyl-, ethyl ester
 (6CI, 7CI, 8CI)
 OTHER NAMES:
 CN 1-(3-Cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid ethyl
 ester
 CN **Diphenoxylate**
 FS 3D CONCORD
 MF C30 H32 N2 O2
 CI COM
 LC STN Files: ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
 BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CBNB, CHEMCATS, CHEMLIST, CIN,
 DDFU, DIOGENES, DRUGU, EMBASE, HSDB*, IPA, MEDLINE, MRCK*, PROMT,
 RTECS*, SPECINFO, TOXCENTER, USAN, USPATFULL
 (*File contains numerically searchable property data)
 Other Sources: EINECS**, WHO
 (**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

105 REFERENCES IN FILE CA (1967 TO DATE)
 2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 105 REFERENCES IN FILE CAPLUS (1967 TO DATE)
 8 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

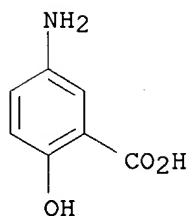
RN 53179-11-6 REGISTRY
 CN 1-Piperidinebutanamide, 4-(4-chlorophenyl)-4-hydroxy-N,N-dimethyl-
 .alpha.,.alpha.-diphenyl- (9CI) (CA INDEX NAME)
 OTHER NAMES:
 CN **Loperamide**
 FS 3D CONCORD
 MF C29 H33 Cl N2 O2
 CI COM
 LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*,
 BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT,
 CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT,
 DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, NIOSHTIC, PHAR, PROMT,
 RTECS*, SPECINFO, TOXCENTER, USAN, USPATFULL, VETU
 (*File contains numerically searchable property data)
 Other Sources: EINECS**, WHO
 (**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

458 REFERENCES IN FILE CA (1967 TO DATE)
 6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 459 REFERENCES IN FILE CAPLUS (1967 TO DATE)

RN 89-57-6 REGISTRY
 CN Benzoic acid, 5-amino-2-hydroxy- (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN Salicylic acid, 5-amino- (8CI)
 OTHER NAMES:
 CN 2-Hydroxy-5-aminobenzoic acid
 CN 3-Carboxy-4-hydroxyaniline
 CN 5-Amino-2-hydroxybenzoic acid
 CN 5-Aminosalicylic acid
 CN 5-ASA
 CN Asacol
 CN Asacolitin
 CN Asacolon
 CN Claversal
 CN Mesacol
 CN **Mesalamine**
 CN Mesalazine
 CN Pentasa
 CN Salofalk
 CN Salozinal
 FS 3D CONCORD
 DR 61513-32-4
 MF C7 H7 N O3
 CI COM
 LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS,
 BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS,
 CHEMINFORMRX, CHEMLIST, CIN, CSCHM, CSNB, DDFU, DIOGENES, DRUGNL,
 DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, GMELIN*, HODOC*, IFICDB, IFIPAT,
 IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, PHAR, PHARMASEARCH, PROMT,
 RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, ULIDAT, USAN, USPATFULL
 (*File contains numerically searchable property data)
 Other Sources: DSL**, EINECS**, TSCA**, WHO
 (**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1240 REFERENCES IN FILE CA (1967 TO DATE)
 62 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 1244 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L14 'ANSWER 8 OF 8 REGISTRY COPYRIGHT 2002 ACS
RN 9031-11-2 REGISTRY
CN Galactosidase, .beta.- (9CI) (CA INDEX NAME)

OTHER NAMES:

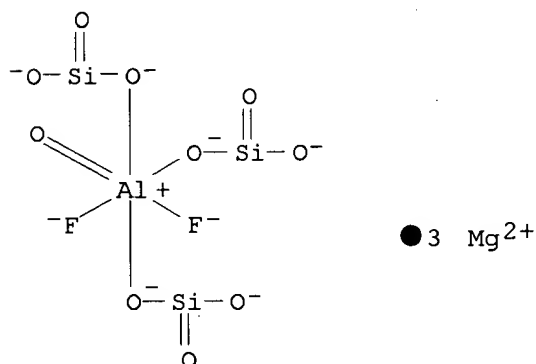
CN .beta.-D-Galactopyranosidase
CN .beta.-D-Galactoside galactohydrolase
CN .beta.-D-Lactosidase
CN .beta.-Galactanase
CN .beta.-Galactosidase
CN .beta.-L-Galactanase
CN .beta.-Lactosidase
CN 11: PN: DE10060140 SEQID: 11 claimed sequence
CN Biolacta
CN Biolacta FN 5
CN E.C. 3.2.1.23
CN **Fungal lactase 30,000**
CN Galactosyl
CN Galantase
CN Hydrolact
CN Lactaid
CN **Lactase**
CN **Lactase F**
CN **Lactase P**
CN **Lactase Y-AO**
CN Lactokanescin G 20x
CN Lactosylceramidase II
CN Lactozyme
CN Lactozyme 3000L
CN LX 5000
CN Maxilact
CN Neutralact
CN Oryzatym
CN p-Nitrophenyl .beta.-galactosidase
CN S 2107
CN Sumiklat
CN Sumylact GLL
CN Sumylact L
CN **Tilactase**
AR 152923-52-9
MF Unspecified
CI COM, MAN

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO,
CA, CABA, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN,
CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MSDS-OHS,
NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS*, TOXCENTER, ULIDAT, USAN,
USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

13550 REFERENCES IN FILE CA (1967 TO DATE)
1107 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
13568 REFERENCES IN FILE CAPLUS (1967 TO DATE)

N 12042-10-3 REGISTRY
 CN Aluminate(7-), difluorotris[metasilicato(2-)-O]oxo-, cesium magnesium
 (1:1:3) (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN **Cesium magnesium aluminosilicate fluoride (CsMg3(Si3AlO10)F2)**
 (8CI)
 CN Magnesium cesium aluminosilicate fluoride, CsMg3(Si3AlO10)F2
 CN Silicic acid (H2SiO3), aluminum complex
 MF Al F2 O10 Si3 . Cs . 3 Mg
 CI CCS
 LC STN Files: CAOLD



● 3 Mg²⁺

● Cs⁺

2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L24 ANSWER 28 OF 32 REGISTRY COPYRIGHT 2002 ACS
 RN 12026-18-5 REGISTRY
 CN Aluminum magnesium oxide silicate (Al4Mg2O3(SiO3)5) (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN Aluminate(4-), pentakis[metasilicato(2-)]trioxotetra-, magnesium (1:2)
 CN Aluminosilicic acid (H4Al4Si5O18), magnesium salt (1:2) (8CI)
 CN **Magnesium aluminosilicate (Mg2Al4Si5O18) (6CI, 7CI)**
 CN Silicic acid (H2SiO3), aluminum complex
 OTHER NAMES:
 CN Aluminum magnesium silicate (Al4Mg2Si5O18)
 CN Artal 23
 CN Silicic acid (H16Si5O18), aluminum magnesium salt (1:4:2)
 DR 39326-53-9, 39343-65-2
 MF Al . Mg . O3 Si . O
 AF Al4 Mg2 O18 Si5
 CI COM, TIS
 LC STN Files: CA, CAOLD, CAPLUS, CASREACT, IFICDB, IFIPAT, IFIUDB,
 TOXCENTER, USPATFULL

Component	Ratio	Component Registry Number
O	3	17778-80-2
O3Si	5	15593-90-5
Mg	2	7439-95-4
Al	4	7429-90-5

530 REFERENCES IN FILE CA (1967 TO DATE)
 8 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 532 REFERENCES IN FILE CAPLUS (1967 TO DATE)
 16 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L24 ANSWER 29 OF 32 REGISTRY COPYRIGHT 2002 ACS
 RN 12026-11-8 REGISTRY
 CN Aluminum magnesium oxide silicate (Al₂MgO₂(SiO₄)) (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN Aluminosilicic acid (H₂Al₂SiO₆), magnesium salt (1:1)
 CN **Magnesium aluminosilicate (MgAl₂SiO₆) (7CI)**
 CN Silicic acid (H₄SiO₄), aluminum complex
 OTHER NAMES:
 CN Aluminum magnesium silicon oxide (Al₂MgSiO₆)
 CN Magnesium aluminum silicate (MgAl₂SiO₆)
 CN Tomix AD 300
 DR 1344-26-9
 MF Al . Mg . O₄ Si . O
 AF Al₂ Mg O₆ Si
 CI COM, TIS
 LC STN Files: CA, CAOLD, CAPLUS, USPATFULL

Component	Ratio	Component Registry Number
O	2	17778-80-2
O ₄ Si	1	17181-37-2
Mg	1	7439-95-4
Al	2	7429-90-5

19 REFERENCES IN FILE CA (1967 TO DATE)
 3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 19 REFERENCES IN FILE CAPLUS (1967 TO DATE)
 4 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L24 ANSWER 30 OF 32 REGISTRY COPYRIGHT 2002 ACS
 RN 11139-40-5 REGISTRY
 CN Aluminum magnesium oxide silicate (Al₂MgO(SiO₃)₃) (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN Aluminosilicic acid (H₂Al₂Si₃O₁₀), magnesium salt (1:1)
 CN Silicic acid (H₂SiO₃), aluminum complex
 OTHER NAMES:
 CN Aluminum magnesium silicate (Al₂MgSi₃O₁₀)
 CN **Magnesium aluminosilicate (MgAl₂Si₃O₁₀)**
 DR 12511-59-0
 MF Al . Mg . O₃ Si . O
 AF Al₂ Mg O₁₀ Si₃
 CI TIS
 LC STN Files: CA, CAPLUS, IPA, USPATFULL

Component	Ratio	Component Registry Number
O	1	17778-80-2
O ₃ Si	3	15593-90-5
Mg	1	7439-95-4
Al	2	7429-90-5

14 REFERENCES IN FILE CA (1967 TO DATE)
 14 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L24 ANSWER 31 OF 32 REGISTRY COPYRIGHT 2002 ACS
 RN 11089-88-6 REGISTRY
 CN Aluminum magnesium oxide silicate (Al₂MgO(Si₂O₅)₃) (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN Aluminate(1-), octaoxotrisilicate-, magnesium (2:1)
 CN Aluminosilicic acid (HAlSi₃O₈), magnesium salt (8CI)
 CN **Magnesium aluminosilicate (MgAl₂Si₆O₁₆) (6CI)**
 OTHER NAMES:
 CN Magnesium aluminum silicate (MgAl₂Si₆O₁₆)
 MF Al . Mg . O₅ Si₂ . O
 AF Al₂ Mg O₁₆ Si₆
 CI TIS
 LC STN Files: CA, CAOLD, CAPLUS

Component	Ratio	Component Registry Number
O ₅ Si ₂	3	20328-07-8
O	1	17778-80-2
Mg	1	7439-95-4
Al	2	7429-90-5

3 REFERENCES IN FILE CA (1967 TO DATE)
 3 REFERENCES IN FILE CAPLUS (1967 TO DATE)
 1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=>

CN Avicel PH 200
 CN **Prosolv 50**
 ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for
 DISPLAY
 DR 12656-52-9, 9012-19-5, 9037-50-7, 9076-30-6, 58968-67-5, 99331-82-5,
 67016-75-5, 67016-76-6, 51395-76-7, 61991-21-7, 61991-22-8, 68073-05-2,
 70225-79-5, 74623-16-8, 75398-83-3, 77907-70-1, 84503-75-3, 89468-66-6,
 39394-43-9
 MF Unspecified
 CI PMS, COM, MAN
 PCT Manual registration, Polyother, Polyother only
 LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO,
 CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST,
 CHEMSAFE, CIN, CSCHM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB,
 IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC,
 PIRA, PROMT, RTECS*, TOXCENTER, TULSA, ULIDAT, USAN, USPAT2, USPATFULL,
 VTB
 (*File contains numerically searchable property data)
 Other Sources: DSL**, EINECS**, TSCA**
 (**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
 56144 REFERENCES IN FILE CA (1967 TO DATE)
 6961 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 56239 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> file caplus		
COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	13.50	15.81

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FILE COVERS 1907 - 22 Aug 2002 VOL 137 ISS 8
 FILE LAST UPDATED: 21 Aug 2002 (20020821/ED)

This file contains CAS Registry Numbers for easy and accurate
 substance identification.

CAS roles have been modified effective December 16, 2001. Please
 check your SDI profiles to see if they need to be revised. For
 information on CAS roles, enter HELP ROLES at an arrow prompt or use
 the CAS Roles thesaurus (/RL field) in this file.

=> s 8050-81-5/rn or simethicone
 189 8050-81-5
 2 8050-81-5D

```

187 8050-81-5/RN
      (8050-81-5 (NOTL) 8050-81-5D )
227 SIMETHICONE
L3    255 8050-81-5/RN OR SIMETHICONE

=> s 12511-31-8/rn or magnesium aluminosilicate
152 12511-31-8
      6 12511-31-8D
147 12511-31-8/RN
      (12511-31-8 (NOTL) 12511-31-8D )
324630 MAGNESIUM
      84 MAGNESIUMS
324672 MAGNESIUM
      (MAGNESIUM OR MAGNESIUMS)
29353 ALUMINOSILICATE
12204 ALUMINOSILICATES
34251 ALUMINOSILICATE
      (ALUMINOSILICATE OR ALUMINOSILICATES)
1705 MAGNESIUM ALUMINOSILICATE
      (MAGNESIUM(W)ALUMINOSILICATE)
L4    1842 12511-31-8/RN OR MAGNESIUM ALUMINOSILICATE

=> s 212693-81-7/rn or 9004-34-6/rn or prosolv
18 212693-81-7
      0 212693-81-7D
18 212693-81-7/RN
      (212693-81-7 (NOTL) 212693-81-7D )
56266 9004-34-6
      6978 9004-34-6D
50217 9004-34-6/RN
      (9004-34-6 (NOTL) 9004-34-6D )
      23 PROSOLV
L5    50223 212693-81-7/RN OR 9004-34-6/RN OR PROSOLV

=> s 13 and 14
L6    0 L3 AND L4

=> s 13 and 15
L7    36 L3 AND L5

=> s 14 and 15
L8    21 L4 AND L5

=> s 76824-35-6/rn or famotidine
1032 76824-35-6
      33 76824-35-6D
1012 76824-35-6/RN
      (76824-35-6 (NOTL) 76824-35-6D )
1259 FAMOTIDINE
L9    1318 76824-35-6/RN OR FAMOTIDINE

=> s 179474-81-8/rn or prucalopride
23 179474-81-8
      0 179474-81-8D
23 179474-81-8/RN
      (179474-81-8 (NOTL) 179474-81-8D )
31 PRUCALOPRIDE
L10   32 179474-81-8/RN OR PRUCALOPRIDE

=> s 915-30-0/rn or diphenoxylate
105 915-30-0
      3 915-30-0D

```

```

102 915-30-0/RN
    (915-30-0 (NOTL) 915-30-0D )
139 DIPHENOXYLATE
L11 163 915-30-0/RN OR DIPHENOXYLATE

=> s 53179-11-6/rn or looperamide
    459 53179-11-6
    7 53179-11-6D
    452 53179-11-6/RN
        (53179-11-6 (NOTL) 53179-11-6D )
    619 LOPERAMIDE
L12 638 53179-11-6/RN OR LOPERAMIDE

```

```

=> s 89-57-6/rn or mesalamine
    1244 89-57-6
    63 89-57-6D
    1204 89-57-6/RN
        (89-57-6 (NOTL) 89-57-6D )
    112 MESALAMINE
L13 1219 89-57-6/RN OR MESALAMINE

```

```

=> s 9031-11-2/rn or lactase
    13573 9031-11-2
    1107 9031-11-2D
    12542 9031-11-2/RN
        (9031-11-2 (NOTL) 9031-11-2D )
    3119 LACTASE
    48 LACTASES
    3132 LACTASE
        (LACTASE OR LACTASES)
L14 13637 9031-11-2/RN OR LACTASE

```

```

=> s 13 and 19
L15 19 L3 AND L9

```

```

=> s 13 and (110 or 111 or 112 or 114)
L16 14 L3 AND (L10 OR L11 OR L12 OR L14)

```

```

=> d his

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(FILE 'HOME' ENTERED AT 09:32:33 ON 22 AUG 2002)

FILE 'REGISTRY' ENTERED AT 09:39:15 ON 22 AUG 2002

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L1 1 S NEUSILIN
L2 2 S PROSOLV

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FILE 'CAPLUS' ENTERED AT 09:40:24 ON 22 AUG 2002

```

L3 255 S 8050-81-5/RN OR SIMETHICONE
L4 1842 S 12511-31-8/RN OR MAGNESIUM ALUMINOSILICATE
L5 50223 S 212693-81-7/RN OR 9004-34-6/RN OR PROSOLV
L6 0 S L3 AND L4
L7 36 S L3 AND L5
L8 21 S L4 AND L5
L9 1318 S 76824-35-6/RN OR FAMOTIDINE
L10 32 S 179474-81-8/RN OR PRUCALOPRIDE
L11 163 S 915-30-0/RN OR DIPHENOXYLATE
L12 638 S 53179-11-6/RN OR LOPERAMIDE
L13 1219 S 89-57-6/RN OR MESALAMINE
L14 13637 S 9031-11-2/RN OR LACTASE
L15 19 S L3 AND L9
L16 14 S L3 AND (L10 OR L11 OR L12 OR L14)

```

=> s 116 or 115
L17 23 L16 OR L15

=> s 117 and 14
L18 0 L17 AND L4

=> s 117 and 15
L19 3 L17 AND L5

=> d ibib abs hitrn 1-3

L19 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:534969 CAPLUS
DOCUMENT NUMBER: 133:140262
TITLE: Slow-release pharmaceutical compositions
INVENTOR(S): Huber, Gerald; Gruber, Peter
PATENT ASSIGNEE(S): Losan Pharma G.m.b.H., Germany
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000044353	A1	20000803	WO 1999-IB180	19990129
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
AU 9919808	A1	20000818	AU 1999-19808	19990129
EP 1146862	A1	20011024	EP 1999-900623	19990129
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI			
BR 9916972	A	20011106	BR 1999-16972	19990129
NO 2001003336	A	20010925	NO 2001-3336	20010705

PRIORITY APPLN. INFO.: WO 1999-IB180 A 19990129

AB A pharmaceutical compn. for the slow release of an active agent in the gastrointestinal tract comprises multiple particles which contain an active agent and which are coated with a material that is insol. in gastrointestinal juice. The particles have a core consisting of a homogeneous mixt. of pharmaceutical active agent and a polymer which is insol. in gastrointestinal juice, with a max. av. inner pore diam. of 35 .mu.m. The compn. enables an efficient release which is independent of pH, even with comparatively small quantities of polymer, and has good stability during storage. Thus, a mixt. of 5-aminosalicylic acid (I) 175, Eudragit RS30D 29.167, and tri-Et citrate 1.750 kg was granulated with 7.65 kg H2O, dried at 50-90.degree., compacted, coated with a suspension contg. Eudragit NE40D 20.869, talc 4.435, 33% **simethicone** antifoam emulsion 0.509, and H2O 20.867 kg, and 198.450 kg of the coated granules (max. size 1000 .mu.m) were mixed with microcryst. cellulose 50.421, Kollidon K90 3.129, and Kollidon CL 14.000 kg in a cyclone granulator and compressed into 760-mg tablets each contg. 500.00 mg I. These tablets released 24.9 and 82.5% of their I content after 30 and 240 min, resp., at pH 1.2.

IT **9004-34-6**, Cellulose, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(microcryst.; slow-release pharmaceutical compns.)

IT 76824-35-6, Famotidine

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(slow-release pharmaceutical compns.)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:259972 CAPLUS

DOCUMENT NUMBER: 132:293042

TITLE: Encapsulation of sensitive liquid components into a matrix to obtain discrete shelf-stable particles

INVENTOR(S): Van Lengerich, Bernhard H.

PATENT ASSIGNEE(S): General Mills, Inc., USA

SOURCE: PCT Int. Appl., 56 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000021504	A1	20000420	WO 1999-US20905	19991006
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
AU 9963872	A1	20000501	AU 1999-63872	19991006
EP 1119345	A1	20010801	EP 1999-951433	19991006
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
NO 2000004784	A	20000925	NO 2000-4784	20000925
PRIORITY APPLN. INFO.:			US 1998-103700P	P 19981009
			US 1998-109696P	P 19981124
			US 1999-233443	A 19990120
			US 1998-79060P	P 19980323
			WO 1999-US4267	W 19990323
			WO 1999-US20905	W 19991006

AB A liq. encapsulant component which contains an active, sensitive encapsulant, such as a live microorganism or an enzyme dissolved or dispersed in a liq. plasticizer is admixed with a plasticizable matrix material. The matrix material is plasticizable by the liq. plasticizer and the encapsulation of the active encapsulant is accomplished at a low temp. and under low shear conditions. The active component is encapsulated and/or embedded in the plasticizable matrix component or material in a continuous process to produce discrete, solid particles. The liq. content of the liq. encapsulant component provides substantially all or completely all of the liq. plasticizer needed to plasticize the matrix component to obtain a formable, extrudable, cuttable, mixt. or dough. Removal of liq. plasticizer prior to extrusion is not needed to adjust the viscosity of the mixt. for formability. Release of an active component from the matrix may be delayed or controlled over time so that the active component is delivered when and where it is needed to perform its intended function. Controlled release, discrete, solid particles

which contain an encapsulated and/or embedded component such as a heat sensitive or readily oxidizable pharmaceutically, biol., or nutritionally active component are continuously produced without substantial destruction of the matrix material or encapsulant.

IT **8050-81-5, Simethicone 9004-34-6, Cellulose,**
biological studies **53179-11-6, Loperamide**
76824-35-6, Famotidine

RL: FFD (Food or feed use); BIOL (Biological study); USES (Uses)
(encapsulation of sensitive liq. components into matrix to obtain
discrete shelf-stable particles)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1993:588597 CAPLUS

DOCUMENT NUMBER: 119:188597

TITLE: Taste-masked pharmaceutical suspensions containing
xanthan gum and microcrystalline cellulose

INVENTOR(S): Blase, Cynthia M.; Shah, Manoj N.

PATENT ASSIGNEE(S): McNeil-PPC, Inc., USA

SOURCE: Eur. Pat. Appl., 11 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 556057	A1	19930818	EP 1993-301018	19930212
EP 556057	B1	19961009		
R: BE, CH, ES, FR, GB, IT, LI, NL				
US 5272137	A	19931221	US 1992-835877	19920214
AU 9332924	A1	19930819	AU 1993-32924	19930209
AU 671610	B2	19960905		
CA 2089430	AA	19930815	CA 1993-2089430	19930212
CA 2089430	C	19980421		
ES 2095566	T3	19970216	ES 1993-301018	19930212
US 5409907	A	19950425	US 1993-168605	19931216

PRIORITY APPLN. INFO.: US 1992-835877 19920214

AB The title compn. contains a pharmaceutical active ingredient, e.g.
acetaminophen (I) 0.2-20, xanthan gum 0.12-0.2 and microcryst. cellulose
0.6-1.0%. Formulation of a suspension of I is given.

IT **9004-34-6, Cellulose, biological studies**

RL: BIOL (Biological study)

(microcryst., taste-masked pharmaceutical suspensions contg.)

IT **8050-81-5, Simethicone 76824-35-6**

RL: BIOL (Biological study)

(taste-masked pharmaceutical suspensions contg. cellulose and xanthan
gum and)

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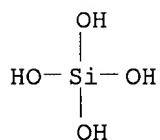
NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2	Apr 08	"Ask CAS" for self-help around the clock
NEWS	3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS	4	Apr 09	ZDB will be removed from STN
NEWS	5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS	6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS	7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS	8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS	9	Jun 03	New e-mail delivery for search results now available
NEWS	10	Jun 10	MEDLINE Reload
NEWS	11	Jun 10	PCTFULL has been reloaded
NEWS	12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS	13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS	14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS	15	Jul 30	NETFIRST to be removed from STN
NEWS	16	Aug 08	CANCERLIT reload
NEWS	17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS	18	Aug 08	NTIS has been reloaded and enhanced
NEWS	19	Aug 09	JAPIO to be reloaded August 25, 2002
NEWS	20	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS	21	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS	22	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS EXPRESS			February 1 CURRENT WINDOWS VERSION IS V6.0d, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
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NEWS INTER			General Internet Information
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L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
 RN 12511-31-8 REGISTRY
 CN Silicic acid (H4SiO4), aluminum magnesium salt (2:2:1) (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN Aluminosilicic acid (HAlSiO4), magnesium salt (8CI)
 CN Magnesium aluminosilicate (MgAl2Si2O8) (6CI, 7CI)
 OTHER NAMES:
 CN Aluminum magnesium silicate
 CN Angast
 CN Magnesium aluminate metasilicate
 CN Magnesium aluminosilicate (Mg(AlSiO4)2)
 CN Magnesium aluminum silicate (MgAl2(SiO4)2)
 CN Magnesium aluminum silicate (MgAl2Si2O8)
 CN **Neusilin**
 CN **Neusilin FH 2**
 CN **Neusilin FL 2**
 CN **Neusilin UFL 2**
 CN **Neusilin US2**
 DR 24716-65-2, 50958-44-6, 37303-22-3, 107497-93-8
 MF Al . H4 O4 Si . 1/2 Mg
 CI COM
 LC STN Files: BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CHEMLIST, CIN, DDFU, DRUGU, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUIDB, MRCK*, PROMT, TOXCENTER, USPATFULL
 (*File contains numerically searchable property data)
 Other Sources: EINECS**
 (**Enter CHEMLIST File for up-to-date regulatory information)
 CRN (10193-36-9)



Al

1/2 Mg

152 REFERENCES IN FILE CA (1967 TO DATE)
 6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 153 REFERENCES IN FILE CAPLUS (1967 TO DATE)
 3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> s prosolv

L2 2 PROSOLV

=> d 1-2

L2 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2002 ACS
 RN 212693-81-7 REGISTRY

CN Cellulose, mixt. with silica (9CI) (CA INDEX NAME)
OTHER NAMES:
CN ProSolv
CN ProSolv 90
CN ProSolv SMCC 50
CN ProSolv SMCC 90
MF O2 Si . Unspecified
CI MXS
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 7631-86-9
CMF O2 Si

O=Si=O

18 REFERENCES IN FILE CA (1967 TO DATE)
18 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L2 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2002 ACS
RN 9004-34-6 REGISTRY
CN Cellulose (8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN .alpha.-Cellulose
CN .beta.-Amylose
CN 3mAQUACEL
CN 402-2B
CN Alicell LV
CN Alpha Cel PB 25
CN Alphafloc
CN Arbocel
CN Arbocel B 00
CN Arbocel B 600
CN Arbocel B 600/30
CN Arbocel B 800
CN Arbocel B 820C
CN Arbocel BC 1000
CN Arbocel BC 200
CN Arbocel BE 600
CN Arbocel BE 600/10
CN Arbocel BE 600/20
CN Arbocel BE 600/30
CN Arbocel BEM
CN Arbocel BFC 200
CN Arbocel BW 40
CN Arbocel DC 1000
CN Arbocel FD 00
CN Arbocel FD 600/30
CN Arbocel FIC 200
CN Arbocel FT 40

CN Arbocel FT 600/30H
CN Arbocel TF 30HG
CN Arbocel TP 40
CN Avicel
CN Avicel 101
CN Avicel 102
CN Avicel 2330
CN Avicel 2331
CN Avicel 955
CN Avicel CL 611
CN Avicel E 200
CN Avicel F 20
CN Avicel FD 100
CN Avicel FD 101
CN Avicel FD-F 20
CN Avicel M 06
CN Avicel M 15
CN Avicel M 25
CN Avicel NT 020
CN Avicel PH 101
CN Avicel PH 102
CN Avicel PH 105
CN Avicel PH 200
CN **Prosolv 50**

ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for
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DR 12656-52-9, 9012-19-5, 9037-50-7, 9076-30-6, 58968-67-5, 99331-82-5,
67016-75-5, 67016-76-6, 51395-76-7, 61991-21-7, 61991-22-8, 68073-05-2,
70225-79-5, 74623-16-8, 75398-83-3, 77907-70-1, 84503-75-3, 89468-66-6,
39394-43-9

MF Unspecified

CI PMS, COM, MAN

PCT Manual registration, Polyother, Polyother only

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO,
CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST,
CHEMSAFE, CIN, CSCHM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB,
IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC,
PIRA, PROMT, RTECS*, TOXCENTER, TULSA, ULIDAT, USAN, USPAT2, USPATFULL,
VTB

(*File contains numerically searchable property data)

Other Sources: DSL**, EINECS**, TSCA**

(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

56144 REFERENCES IN FILE CA (1967 TO DATE)

6961 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

56239 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=>

ACCESSION NUMBER: 82:20199 USPATFULL
 TITLE: Compressed chewable antacid tablet and method for forming same
 INVENTOR(S): Puglia, Wayne J., Bellerose Village, NY, United States
 Patanasinth, Kanit J., Tarrytown, NY, United States
 Lombardo, Andrew T., Bronx, NY, United States
 Beam, John E., Norwalk, CT, United States
 Mackay, Donald A. M., Pleasantville, NY, United States
 PATENT ASSIGNEE(S): Life Savers, Inc., New York, NY, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4327076		19820427
APPLICATION INFO.:	US 1980-207157		19801117 (6)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Rose, Shep K.		
LEGAL REPRESENTATIVE:	Kornutik, Richard		
NUMBER OF CLAIMS:	5		
EXEMPLARY CLAIM:	1		
LINE COUNT:	553		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB An improved compressed soft chewable tablet is provided, which may contain an antacid or other active ingredient, has good flexibility, is breakage resistant and disintegrates immediately upon chewing. The tablet of the invention is formed of particles of antacid and/or other active ingredient which are isolated from other ingredients of the tablet, preferably by admixing particles of active ingredient with particles formed of edible fat or oil absorbed on a fat-absorbing material, such as microcrystalline cellulose and blending such particles with one or more tablet bonders; the tablet also includes additional amounts of tablet bonders, flavors and other conventional tableting aids to help in making the tablet more palatable. Upon chewing, the tablet is quickly converted to a smooth creamy non-gritty palatable emulsion.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT Oils
 (almond, compressed chewable antacid tablets contg. fat absorbing materials and)
 IT Coconut oil
 IT Corn oil
 IT Cottonseed oil
 IT Fats, biological studies
 IT Linseed oil
 IT Olive oil
 IT Peanut oil
 IT Safflower oil
 IT Soybean oil
 (compressed chewable antacid tablets contg. fat absorbing materials and)
 IT Tallow
 (hydrogenated, compressed chewable antacid tablets contg. fat absorbing materials and)
 IT Oils
 (palm, compressed chewable antacid tablets contg. fat absorbing materials and)
 IT Oils
 (sesame, compressed chewable and antacid tablets contg. fat absorbing materials and)
 IT Antacids and Antiflatulents

(tablets, fats and fat absorbing materials for compressed chewable)
IT Oils
(vegetable, hydrogenated, compressed chewable antacid tablets contg.
fat absorbing materials and)
IT Tablets
(chewable, antacid, compressed, fats and fat absorbing materials for)
IT 50-70-4, biological studies 57-50-1, biological studies 69-65-8
87-99-0 **9004-34-6**, biological studies 9004-53-9 9005-25-8,
biological studies
(compressed chewable antacid tablets contg. fatty materials and)

=>

ACCESSION NUMBER: 93:107008 USPATFULL
TITLE: Aqueous pharmaceutical suspension for pharmaceutical
actives
INVENTOR(S): Blase, Cynthia M., Lansdale, PA, United States
Shah, Manoj N., Norristown, PA, United States
PATENT ASSIGNEE(S): McNeil-PFC, Inc., Milltown, NJ, United States (U.S.
corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5272137		19931221
APPLICATION INFO.:	US 1992-835877		19920214 (7)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Griffin, Ronald W.		
NUMBER OF CLAIMS:	12		
EXEMPLARY CLAIM:	1		
LINE COUNT:	612		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to an aqueous pharmaceutical suspension composition comprising: from about 0.2% to 20% of a substantially water soluble pharmaceutical active, e.g. acetaminophen; a suspension stabilizing effective amount of xanthan gum and microcrystalline cellulose; an effective amount of taste masking compositions; and water, as well as a process for producing such aqueous pharmaceutical suspensions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 9004-34-6, Cellulose, biological studies

(microcryst., taste-masked pharmaceutical suspensions contg.)

IT 8050-81-5, Simethicone 76824-35-6

(taste-masked pharmaceutical suspensions contg. cellulose and xanthan gum and)

ACCESSION NUMBER: 95:36382 USPATFULL
 TITLE: Aqueous pharmaceutical suspension for pharmaceutical
 actives
 INVENTOR(S): Blase, Cynthia M., Lansdale, PA, United States
 Shah, Manoj N., Norristown, PA, United States
 PATENT ASSIGNEE(S): McNeil-PPC, Inc., Spring House, PA, United States (U.S.
 corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5409907		19950425
APPLICATION INFO.:	US 1993-168605		19931216 (8)
DISCLAIMER DATE:	20101221		
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1992-835877, filed on 14 Feb 1992, now patented, Pat. No. US 5272137		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Griffin, Ronald W.		
LEGAL REPRESENTATIVE:	Plantz, Bernard F.		
NUMBER OF CLAIMS:	13		
EXEMPLARY CLAIM:	1		
LINE COUNT:	611		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to an aqueous pharmaceutical suspension
 composition comprising: from about 0.2% to 20% of a substantially water
 soluble pharmaceutical active, e.g. acetaminophen; a suspension
 stabilizing effective amount of xanthan gum and microcrystalline
 cellulose; an effective amount of taste masking compositions; and water,
 as well as a process for producing such aqueous pharmaceutical
 suspensions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **9004-34-6**, Cellulose, biological studies
 (microcryst., taste-masked pharmaceutical suspensions contg.)
 IT **8050-81-5**, Simethicone **76824-35-6**
 (taste-masked pharmaceutical suspensions contg. cellulose and xanthan
 gum and)

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Pharmaceutical Patents

Title: Pharmaceutical excipient having improved compressibility

United States Patent: 6,217,909

Inventors: Sherwood; Bob E. (Amenia, NY); Staniforth; John H. (Bath, GB);
 Hunter; Edward A. (Glenham, NY)

Assignee: Edward **Mendell Co., Inc. (Patterson, NY)**

Appl. No.: 438646

Filed: November 12, 1999

Abstract

Calendar

A microcrystalline cellulose-based excipient having improved compressibility, whether utilized in direct compression, dry granulation or wet granulation formulations, is disclosed. The excipient is an agglomerate of microcrystalline cellulose particles and from about 0.1% to about 20% silicon dioxide particles, by weight of the microcrystalline cellulose, wherein the microcrystalline cellulose and silicon dioxide are in intimate association with each other. The silicon dioxide utilized in the novel excipient has a particle size from about 1 nanometer to about 100 microns. Most preferably, the silicon dioxide is a grade of colloidal silicon dioxide.

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OBJECTS AND SUMMARY OF THE INVENTION

It is an object of the present invention to provide an excipient which is useful in a variety of applications, and which may be utilized in direct compression or wet granulation methods.

It is a further object of the present invention to provide an excipient useful in

direct compression methods which has improved compressibility relative to microcrystalline cellulose.

It is a further object of the present invention to provide an excipient useful in wet granulation methods which has improved compressibility relative to microcrystalline cellulose.

It is a further object of the present invention to provide a free-flowing excipient which has excellent compressibility properties when utilized in direct compression or wet granulation methods, and which furthermore possesses pharmaceutically acceptable disintegration properties.

It is a further object of the present invention to provide an improved microcrystalline cellulose excipient in which the microcrystalline cellulose has not been chemically altered, and which has improved compressibility relative to "off-the-shelf" commercially available microcrystalline cellulose.

It is a further object of the present invention to provide a solid dosage form which includes one or more active ingredients and the improved microcrystalline cellulose excipient of the present invention.

It is a further object of the present invention to provide an oral solid dosage form for one or more drugs which is economical to manufacture, which maintains its integrity during storage, and which possesses excellent disintegration and dissolution properties when exposed, e.g., to gastrointestinal fluid.

In accordance with the above objects and others which will be obvious to those skilled in the art, the present invention is directed to an excipient comprising a particulate agglomerate of coprocessed microcrystalline cellulose and from about 0.1% to about 20% silicon dioxide, by weight of the microcrystalline cellulose, the microcrystalline cellulose and silicon dioxide being in intimate association with each other, and the silicon dioxide portion of the agglomerate being derived from a silicon dioxide having a particle size from about 1 nanometer (nm) to about 100 microns (μm), based on average primary particle size.

In preferred embodiments, the silicon dioxide comprises from about 0.5% to about 10% of the excipient, and most preferably from about 1.25% to about 5% by weight relative to the microcrystalline cellulose.

In additional preferred embodiments of the invention, the silicon dioxide has a particle size from about 5 nm to about 40 μm , and most preferably from about 5 nm to about 50 μm .

In preferred embodiments of the present invention, the silicon dioxide is further characterized by a surface area from about $10 \text{ m}^2/\text{g}$ to about $500 \text{ m}^2/\text{g}$, preferably from about $50 \text{ m}^2/\text{g}$ to about $500 \text{ m}^2/\text{g}$, and more preferably from about $175 \text{ m}^2/\text{g}$ to about $350 \text{ m}^2/\text{g}$.

The present invention is further directed to an aqueous slurry useful in the preparation of a compressible excipient useful in dry and wet granulation formulation methods, comprising a mixture of microcrystalline cellulose and from about 0.1% to about 20% silicon dioxide, by weight relative to the microcrystalline cellulose, the silicon dioxide having a particle size from about 1 nm to about 100 .mu.m. The solids content of the aqueous slurry is from about 0.5% to about 25%, by weight, preferably from about 15% to about 20% by weight, and most preferably from about 17% to about 19% by weight.

The present invention is further directed to a mixture of an active ingredient(s) and an excipient comprising a particulate agglomerate of coprocessed microcrystalline cellulose and from about 0.1% to about 20% silicon dioxide, by weight of the microcrystalline cellulose, the microcrystalline cellulose and silicon dioxide being in intimate association with each other, and the silicon dioxide having a particle size from about 1 nm to about 100 .mu.m. The ratio of active ingredient to excipient is from about 1:99 to about 99:1, by weight.

The present invention is further directed to a granulate of an active ingredient(s) and the novel excipient described herein, wherein the active ingredient(s) and excipient have been subjected to a wet granulation procedure.

The present invention is further directed to a compressed solid dosage form comprising an active ingredient(s) and the novel excipient described herein, wherein the active ingredient(s) and excipient have been directly compressed into the solid dosage form or have been subjected to a wet granulation procedure and thereafter compressed into the solid dosage form. The compressed solid dosage form provides a suitable immediate release dissolution profile of the active ingredient(s) when exposed to aqueous solutions during invitro dissolution testing, and provides a release of drug in an environment of use which is considered bioavailable. In further embodiments of the invention, the dissolution profile of the solid dosage form is modified to provide a controlled or sustained release dissolution profile.

The present invention is further directed to a method of maintaining and/or enhancing the compressibility of microcrystalline cellulose. The method includes forming an aqueous slurry containing a mixture of microcrystalline cellulose and silicon dioxide having a particle size from about 1 nm to about 100 .mu.m, and drying the slurry to obtain microcrystalline cellulose-based excipient particles in which the silicon dioxide particles have been integrated with the microcrystalline cellulose particles. Within this aspect of the invention, the slurry contains from about 0.5% to about 25% by weight microcrystalline cellulose, with amounts of from about 15% to about 20% being preferred. Furthermore, the slurry contains from about 0.25% to about 5% by weight silicon dioxide.

The novel excipient described herein is free-flowing, possesses excellent

disintegration properties, and importantly, in certain embodiments possesses improved compressibility relative to normal "off-the-shelf" commercially available microcrystalline cellulose when directly compressed. The advantages of the novel excipient described herein are especially realized in pharmaceutical formulations prepared using wet granulation techniques. When utilized in wet granulation techniques, the novel excipient surprisingly provides a compressibility which is substantially improved in preferred embodiments in comparison to the compressibility of normal "off-the-shelf" commercially available microcrystalline cellulose used in wet granulation and is even comparable to "off-the-shelf" microcrystalline cellulose used in direct compression techniques. In other embodiments, the novel excipient surprisingly provides a compressibility which is substantially superior to the compressibility of normal "off-the-shelf" commercially available microcrystalline cellulose used in direct compression techniques.

Claim 1 of 20 Claims

What is claimed is:

1. An excipient composition comprising a particulate agglomerate of coprocessed microcrystalline cellulose and from about 0.1% to about 20% by weight silicon dioxide, the microcrystalline cellulose and silicon dioxide being in intimate association with each other, said silicon dioxide portion of said agglomerate being derived from a silicon dioxide having an average primary particle size from about 1 nm to about 100 .mu.m, said excipient composition having a bulk density of from about 0.35 g/ml to about 0.6 g/ml.

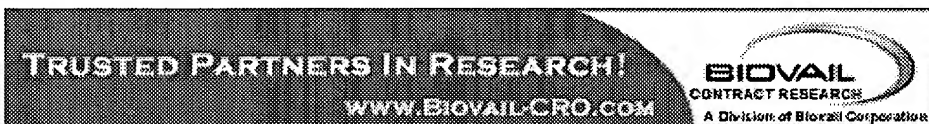
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These search terms have been highlighted: **silicified microcrystalline cellulose**



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Title: Stabilized thyroxine medications

United States Patent: 6,190,696

Inventors: Groenewoud; Pieter J. (4 Westover Ct., Yardley, PA 19067)

Appl. No.: 327256

Filed: June 7, 1999

Abstract

Thyroxine medications which include combinations of levothyroxine, and/or liothyronine, or dextrothyroxine, or thyroid, and one or more iodine salts, or iodine donor compounds are described, which produce a stable thyroxine medication, with a long shelf life. A method for manufacturing the medications is also described.

Calendar

DESCRIPTION OF THE PRIOR AND INVENTION

Various prior art formulations are disclosed in the U.S. Patents to Kummer, et al., U.S. Pat. No. 4,110,470; Miller, et al., U.S. Pat. No. 4,585,652; Anderson, et al., U.S. Pat. No. 4,818,531; Sloan, U.S. Pat. No. 5,001,115; Ginger, et al., U.S. Pat. No. 2,889,363; Ginger, et al., U.S. Pat. No. 2,889,364; Chen, et al. U.S. Pat. No. 5,225,204; and Groenewoud, et al., U.S. Pat. No. 5,635,209.

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In the U.S. Pat. No. 2,889,364; Chen et al., methods are described using poloxamer and other compounds as a stabilizing complex former in combination with levothyroxine and **cellulose compounds. It also describes the use of cellulose compounds alone as the stabilizer in both dry and solvent based processes. A major disadvantage of a wet granulation process in particular when water and heat is used as stated in this patent is that one will have to**

compensate in advance for the degradation that will occur during the process leaving unknown degradation products in the finished stabilized product. The use of cellulose compound to achieve stabilization in dry processes will circumvent this, however the stabilizing effect of cellulose compounds is limited and much less effective than for example Sodium Iodide.

Chen, et al. also teach to avoid the use of lactose and other saccharides since these compounds are known to degrade thyroxine medications more rapidly. Some of these well accepted excipients have very desirable tableting characteristics and can be used in my invention after careful isolation of thyroxine in granules composed of a stabilizing matrix and the active compound. Yet another disadvantage is the use of some of the solvents that are suggested such as methylene dichloride and methanol that are quite toxic and for which the United States Pharmacopoeia XXIII (USP), has extremely low acceptance limits for residues of these substances in the finished product. Current chemical processes mostly avoid chlorinated and other toxic solvents altogether wherever possible. In my new invention only purified water or ethanol is used before contact with thyroxine to avoid initial degradation. In my new invention heat is only used in a process step before the thyroxine or liothyronine is added for the same reason not to cause any initial degradation. Water of course is non-toxic and ethanol has very limited toxicity, if any, at the level used in my invention. Chen et al. also suggests the use of calcium phosphate, calcium carbonate and calcium sulfate. However in a letter (Letters--Mar. 11, 1998) to the Journal of the American Medical Association, researchers report reduction of levothyroxine efficacy if used simultaneously with calcium carbonate. The report further states "Calcium carbonate itself or, alternatively excipients or contaminants in the preparation could form insoluble chelates with levothyroxine."

In my new invention the use of calcium and other multivalent ions is avoided to further improve the stability and efficacy of the medication.

In my prior U.S. Pat. No. 5,635,209 a method is described wherein levothyroxine sodium titration is physically combined with potassium iodide and other ingredients to form a more stable formulation.

While the composition described in U.S. Pat. No. 5,635,209 is suitable for its intended use it has several limitations and disadvantages. For example potassium iodide is used in varying levels ranging from 0.1% to 0.7%. Although the levels suggested for the lower strengths do not exceed recommended daily allowances (RDA) the higher levels do exceed this level. This can potentially lead to undesirable effects caused by excess iodine intake especially when these medications are taken in combination with multivitamin and mineral combinations. For example Flintstones.RTM. multi vitamin tablets for children and other brands contain 150 mcg of iodine which is equivalent to the RDA.

A carefully selected level of iodine compounds in my new invention is less than the daily recommended allowance.

In my new invention only one level is used for the lower as well as the higher strengths and in one particular process described in my new invention far less than the normal daily intake. Yet the stabilizing effect is sufficient to provide significantly improved stability without any concern about the high iodide levels, especially for the pediatric patient population.

Another disadvantage of the use of potassium iodide is the potential of metathesis with Levothyroxine sodium. The potassium from the potassium iodide can potentially take the place of the sodium on the thyroxine molecule and vice versa. This can potentially lead to a change in the dissolution rate and essentially change the compound from the identity claimed on the label of the medication. My new invention describes the use of sodium iodide which does not present this undesirable potential reaction.

Also U.S. Pat. No. 5,635,209 does not include the combination products of levothyroxine sodium and liothyronine sodium or thyroid gland preparation furthermore it only describes the process of stabilizing levothyroxine sodium in the finished product.

My new invention describes a way to stabilize the raw materials itself to increase the flexibility in which the invention can be used as described in the examples of the invention. In addition to the increased flexibility of the use of this stabilized levothyroxine or liothyronine concentrate it brings the level of the suitable iodine salts down to levels that are far less than the RDA and therefore do not add significantly to normal dietary and/or supplemental intake.

Also neither one of the two inventions describe the use of antioxidants. This new invention will show how an antioxidant can be effectively used to further aid in the stabilization of the said medications.

Levothyroxine Sodium and Liothyronine Sodium Stability

The instability of levothyroxine and liothyronine has been known for a long time. Levothyroxine and liothyronine are degraded through oxidation and/or de-iodination and other excipient/active interactions in which de-iodination appears to be the predominant degradation pathway.

Of interest is the article by Rapaka et al. that describes the difference between the stability of liothyronine and levothyroxine. The two co-valently bound iodine atoms in the 1 and 5 position are the least stable, once 1 iodine atom becomes detached the resulting compound is even less stable and more likely to lose the second iodine atom.

The invention demonstrates that levothyroxine and liothyronine can be stabilized by embedding the active particles in a matrix that contains an effective stabilizer in the form of an iodide salt of for example sodium. The resulting action is stabilization of the levothyroxine particle without it being necessary that the stabilizing agents interact by surrounding the individual thyroxine molecules.

One would expect to see better stabilizing action the more iodide is used however an optimum concentration is reached around 0.1% iodide and above approximately 0.3% iodide in a 100 mg tablet containing 100 mcg levothyroxine sodium it starts to interfere with the stability of the active compound.

Since another degradation pathway is oxidation the addition of a specially prepared antioxidant will further aid in the stabilization of levothyroxine sodium and liothyronine sodium.

Further degradation can be prevented through careful selection of excipients that have proper tableting or encapsulation characteristics without exerting destabilizing effects on the active compounds.

Such compounds are for example but not limited to:

Microcrystalline cellulose, especially newly introduced grades by FMC: Avicel.RTM. (brand name of microcrystalline cellulose) PH-112, and low moisture grade specifically developed for moisture sensitive products with a mean particle size of 90 micron this grade is free flowing to facilitate tableting with good weight control. Avicel PH-113, also low moisture but with a smaller particle size to better facilitate wet granulations with for example alcohol. Avicel.RTM. PH-200 is a large particle grade specifically used as a tableting binder with superior flow characteristics. Avicel.RTM. PH-301, PH302 and the older products PH-101, PH-102 can also be used in a satisfactory manner although the older grades may have some minor disadvantages as it relates to product flow and moisture content. The most recent innovation in the microcrystalline cellulose product line is Ceolus.RTM., also introduced by FMC. Ceolus.RTM. can be used to produce hard tablets because of its flatter structure than regular microcrystalline cellulose; it is prepared from wood pulp from specially selected grades of wood.

Mendel offers a similar product line for microcrystalline cellulose, as Emcocel.RTM. and generic equivalents for the older types are also available. Grades of microcrystalline are typically used as dry binders in tableting, in wet granulations since they can absorb significant quantities of liquids because of their porous structure, as diluents in powders for encapsulation and as carriers for actives and or excipients.

Grades of microcrystalline cellulose also exert some disintegration properties and are considered chemically inert towards most active ingredients.

A newly introduced innovation by Mendel is Prosolv.TM. or silicified microcrystalline cellulose, which is a highly compressible co-processed combination of microcrystalline cellulose with colloidal silicon dioxide.

It has superior tableting characteristics and is offered in two grades, one for wet granulations (Prosolv SMCC.TM.50) and one as a dry binder/diluent (Prosolv SMCC.TM.90). Although it has different characteristics compared

to regular microcrystalline cellulose it has retained all desired properties of these compounds.

As disintegrant several compounds can be used such as sodium starch glycolate especially Explotab.RTM. CLV, that through high cross linking has a lower viscosity than the regular grade and has a more robust disintegration action compared to regular sodium starch glycolate.

Another suitable disintegrant is Emcosoy.RTM. offered by Mendel as a kosher product. Encosoy.RTM. consists of soy polysaccharides and a non-ionic effective disintegrant. Alginate acid is another disintegrant that may be used. Mendel offers alginate acid under the trade name Satialgine.TM. H8.

As lubricant magnesium stearate or other stearates may be used however the preferred lubricant is Sodium Stearyl Fumarate since it does not have the potential to chelate the levothyroxine sodium by donating multi valent alkali or other metal ions.

Mendel offers Stearyl Fumarate sodium under the trade name Pruv.TM.. Another useful lubricant is hydrogenated vegetable oil, offered by Mendel under the name Lubritab.RTM.. Lubritab.RTM. is chemically less reactive than other commonly used lubricants and therefore has excellent formulation compatibility.

Claim 1 of 8 Claims

I claim:

1. A method of making stabilized thyronine medications by combining together

(a) Liothyronine Sodium

(b) at least one iodine salt mixed with a carrier

(c) a disintegrant

(d) a lubricant

(e) a binder, and

(f) a filler.

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Pharmaceutical Patents

Title: Chewable tablet

United States Patent: 6,146,661

Inventors: Hoshino, Kazuaki (Tokyo, JP)

Assignee: Chugai Seiyaku Kabushiki Kaisha (Tokyo, JP)

Appl. No.: 043606

Filed: March 24, 1998

PCT Filed: October 3, 1996

PCT NO: PCT/JP96/02869

Calendar

371 Date: March 24, 1998

102(e) Date: March 24, 1998

PCT PUB.NO.: WO97/12606

PCT PUB. Date: April 10, 1997

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Foreign Application Priority Data: Oct 03, 1995[JP] (7-291612)

Abstract

Chewable tablets prepared by incorporating a sugar alcohol with a dissolution endotherm of 20 calories or more per gram of a gastrointestinally active ingredient such as a mucous membrane repairing agent or an antacid are provided. The

such as a mucous membrane repairing agent or an antacid are provided. The chewable tablets enable the gastrointestinally active ingredient to be orally administered with ease, without water and free from displeasing intrabuccal sensations characteristic of a gastrointestinally active ingredient.

DISCLOSURE OF THE INVENTION

We, the inventors, have conducted in-depth studies to improve the intrabuccal sensations characteristic of chewable tablets as a gastrointestinal drug. These studies have found that this objective can be attained by incorporating not less than a specific amount of a sugar alcohol into the gastrointestinally active ingredient; such a finding led us to accomplish the present invention.

That is, this invention concerns chewable tablets containing a sugar alcohol with a dissolution endotherm of 20 calories or more per gram of a gastrointestinally active ingredient.

The gastrointestinally active ingredient used in the invention may be any pharmaceutically active ingredient for a gastrointestinal drug, such as a mucous membrane repairing agent or an antacid. The particle size of the starting material for the gastrointestinal drug should desirably be small, but any commercially available grade poses no problem. The gastrointestinally active ingredient may be a single ingredient or a mixture of two or more ingredients.

Examples of the mucous membrane repairing agent are sucralfate, sodium azulene sulfonate, aldioxa, glycyrrhizic acid and its salts, L-glutamine, copper chlorophyllin potassium, histidine hydrochloride, porcine gastric wall pepsin decomposition product, and methylmethionine sulfonium chloride.

The antacid includes not only a common antacid generally recognized as being effective in neutralizing gastric acid, but also an H₂ receptor blocking antisecretory effective in healing the gastrointestinal tract. Examples of the antacid are sucralfate, dried aluminum hydroxide gel, **magnesium aluminosilicate, magnesium silicate, synthetic aluminum silicate, synthetic hydrotalcite, magnesium oxide, magnesia alumina hydrate, aluminum hydroxide gel, magnesium hydroxide, sodium bicarbonate, magnesium carbonate, precipitated calcium carbonate, magnesium aluminometasilicate, anhydrous calcium hydrogenphosphate, and calcium hydrogenphosphate.** Examples of the H₂ receptor blocking antisecretory are **ranitidine, cimetidine, famotidine, nizatidine and roxatidine acetate.**

The sugar alcohol used in the invention may be any sugar alcohol in common use, such as sorbitol, erythritol, xylitol or mannitol. The dissolution endotherm of any of the various sugar alcohols is 24 cal/g for sorbitol, 43 cal/g for erythritol, 35 cal/g for xylitol, or 29 cal/g for mannitol (measured in accordance with the customary method by accurately weighing about 0.5 g of the sugar alcohol, and dissolving it in 20 ml of distilled water at 25°C.).

These sugar alcohols may be used alone or as a mixture of two or more. Any of them is incorporated in such an amount that the dissolution endotherm

will be 20 cal or more per gram of the gastrointestinally active ingredient, whereby gastrointestinal chewable tablets with satisfactory intrabuccal sensation when orally administered can be produced. In the chewable tablets of the invention, the amount of the sugar alcohol incorporated is determined by calculation such that it gives a dissolution endotherm of 20 cal or more per gram of the gastrointestinally active ingredient as described above. The upper limit of the amount of the sugar alcohol incorporated in one chewable tablet is restricted by the size of the tablet and the contents of the ingredients other than the sugar alcohol, including the gastrointestinally active ingredient, in one tablet. Assume that 500 mg of a gastrointestinally active ingredient, 5 mg of an excipient, and 5 mg of a binder are contained, with the rest being xylitol (the sugar alcohol used in the invention), are used in the preparation of 1 g of a chewable tablet in accordance with the invention. In this case, the amount of xylitol incorporated is 490 mg. The dissolution endotherm of the sugar alcohol in the chewable tablet is calculated at 34.3 cal per gram of the gastrointestinally active ingredient.

As noted above, the lower limit of the amount of the sugar alcohol incorporated in the invention is 20 cal as a dissolution endotherm per gram of the gastrointestinally active ingredient in the chewable tablet. Whereas its upper limit is not restricted as far as it is within the range in which chewable tablets can be molded. Within this range, it is possible to select the type and the amount of incorporation of the sugar alcohol in view of the hygroscopicity, sweetness, melting point, price, and so forth. The amount of the sugar alcohol incorporated varies with the type of the gastrointestinally active ingredient used. In the case of a gastrointestinally active ingredient, such as sucralfate, which is incorporated in a high proportion, for example, the amount of the sugar alcohol incorporated expressed in terms of the dissolution endotherm is about 20 to 200 cal, preferably about 20 to 100 cal, per gram of sucralfate. On the other hand, in the case of a gastrointestinally active ingredient, such as azulene, which is incorporated in a low proportion, that amount as the dissolution endotherm is about 20 to 30,000 cal, preferably about 500 to 20,000 cal, per gram of azulene.

For the preparation of the chewable tablets of the invention, additives for use in the production of ordinary tablets may be used, unless they do harm, in addition to the gastrointestinally active ingredient and the sugar alcohol. Examples are pharmaceutically acceptable excipients, binders, lubricants, preservatives, stabilizers, colorants and flavors.

The weight of the chewable tablet of the invention is not restricted. For administration of one tablet once, for instance, the weight of one tablet is preferably about 0.5 to 2.0 g, more preferably 0.8 to 1.5 g.

The method of preparing the chewable tablet of the invention is not restricted, either. An ordinary method for producing tablets can be applied.

Claim 1 of 4 Claims

I claim:

1. A chewable tablet as a gastrointestinal drug composition in the form of a chewable tablet which contains erythritol or a mixture of erythritol and another sugar alcohol, and a gastrointestinally active ingredient, the amount of erythritol or the mixture of erythritol and said sugar alcohol expressed in terms of the dissolution endotherm per gram of the active ingredient being at least 20 cal, wherein the gastrointestinally active ingredient is at least one of

a mucous membrane repairing agent selected from the group consisting of sucralfate, sodium azulene sulfonate, aldioxa, glycyrrhizic acid and its salts, L-glutamine, copper chlorophyllin potassium, histidine hydrochloride, porcine gastric wall pepsin decomposition product, and methylmethionine sulfonium chloride,

an antacid selected from the group consisting of fried aluminum hydroxide gel, magnesium aluminosilicate, magnesium silicate, synthetic aluminum silicate, synthetic hydrotalcite, magnesium oxide, magnesia alumina hydrate, aluminum hydroxide gel, magnesium hydroxide, sodium bicarbonate, magnesium carbonate, precipitated calcium carbonate, magnesium aluminometasilicate, anhydrous calcium hydrogenphosphate, and calcium hydrogenphosphate, or

an H₂ receptor blocking antiseecretory selected from the group consisting of ranitidine, cimetidine, famotidine, nizatidine and roxatidine acetate.

If you want to learn more about this patent, please go directly to the U.S. Patent and Trademark Office Web site to access the full patent.

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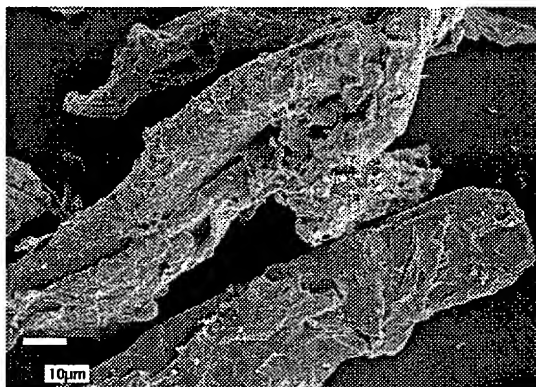
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Amine / MCC interactions

Amine: Organic chemical containing nitrogen, generally represented as $R-NH_2$ (primary amine), $RR'-NH$ (secondary amine) etc.

MCC: Microcrystalline cellulose. A material widely used in the pharmaceutical industry as an excipient (not-drug part of a dosage form) and in the food industry as a thickening agent and general-purpose fat replacer. Basically, purified and dried paper pulp, which is mostly cellulose. Great for all sorts of things, especially making tablets, but there are problems...



Interactions: Drugs that contain an amine functionality (of which there are plenty) have a tendency to bind to MCC. This is normally reversible, but any drug that stays bound to the excipient will not be available to the patient, since you can't digest cellulose. So, this interaction can effectively reduce the dose the patient will receive.

It's a problem because the percent adsorbed increases as concentration decreases. So, if you have a very low dose drug (and some drugs may have an effective dose of about a milligram) you could 'lose' a large amount through adsorption. It's not always financially feasible to increase the amount of drug put in, nor is it good practise, since your *in vitro* tests may not mirror *in vivo* release and patient-to-patient variations will result in different releases of drug, with possible harmful effects.

What I'm doing about it: Trying to find what reduces or increases this interaction. Things such as changing the manufacturer or using a different grade of MCC seem to affect the adsorption of a model drug; that's as much as has been published so far.

Posters and presentations

APV 2002; Florence, Italy. Poster covering some of the adsorption-related aspects of the work. [Download poster \(.pdf, 200K\)](#).

AAPS 2001; Denver, Colorado. Comparison of two different ways of determining the surface energy of MCCs ([Download pdf, 550K](#)). This work was done in collaboration with [SMS UK](#).

Presentation at 20th Pharmaceutical Technology Conference: Showed that, for the batches studied, there are differences in adsorption of tacrine hydrochloride between different manufacturers' products, that high density MCCs adsorb less than standard materials, and that silicified MCC (**SMCC**) adsorbs less drug than the corresponding standard grade. Might not sound exciting, but I won the award for best presentation. There's a photo somewhere to prove it...

More on **MCC** as a compaction aid can be found on [Stephen's homepage](#).

[Fraser's Homepage](#)

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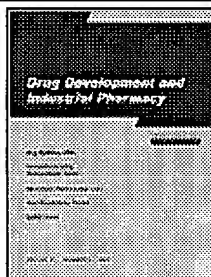
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Journal Article | Print Published: 05/01/2002

Pages 467 - 472

DOI: 10:1081/DDC-120003008

Abstract

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The objective of this study was to investigate the weight and weight uniformity of hard gelatin capsules filled with microcrystalline cellulose (MCC) and silicified microcrystalline cellulose (SMCC) powdered formulations. A tamping-type encapsulation apparatus was used to fill the capsules. The four formulations that were tested included MCC alone, MCC blended with fumed silica, SMCC, and high-density SMCC (SMCC-HD). The mean capsule weight and the average variation in mean capsule weight of each formulation were determined. Both SMCC products exhibited better flow than the MCC alone, with SMCC-HD being the freest flowing of the powders investigated. Capsules filled with the SMCC products had higher fill weights than those containing the MCC powders. The SMCC-containing capsules exhibited the lowest variation in weight, although these findings were not significantly different from either of the MCC-containing capsules. Significantly higher weight variations were found in capsules filled with SMCC-HD. A relationship between Carr's compressibility index and capsule weight variation was found, with more compressible materials producing more uniformly filled capsules. No relationship could be established between powder flow and capsule weight uniformity. These findings suggest that powder flow may not be a critical parameter in ensuring capsule weight uniformity when the encapsulation equipment utilizes a tamping-type filling system.

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Title: Effervescent drug delivery system for oral administration

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United States Patent: 6,391,335

Inventors: Pather; S. Indiran (Plymouth, MN); Robinson; Joseph R. (Madison, WI); Eichman; Jonathan D. (Ann Arbor, MI); Khankari; Rajendra K. (Maple Grove, MN); Hontz; John (Plymouth, MN); Gupte; Sangeeta V. (Maple Grove, MN)

Assignee: Cima Labs Inc. (Minneapolis, MN)

Appl. No.: 613270

Filed: July 10, 2000

Abstract

Calendar

The pharmaceutical compositions of the present invention comprise orally administerable dosage forms that use effervescence as a penetration enhancer for drugs known, or suspected, of having poor bioavailability. Effervescence can occur in the stomach, once the tablet or other dosage form is ingested. In addition to effervescence in the stomach, or as alternative technique, by the use of appropriate coatings and other techniques, the effervescence can occur in other parts of the gastrointestinal tract, including, but not limited to, the esophagus, duodenum, and colon. The site of effervescence and drug release is chosen to correspond with the segment of the gastrointestinal tract displaying maximal absorption of the formulated drug, or to gain some other therapeutic **advantage**.

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DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The pharmaceutical compositions of the present invention comprise orally administerable medicaments in combination with an effervescent as a

penetration enhancer for influencing absorption of a drug in the gastrointestinal tract. Effervescence leads to an increase in the rate and/or the extent of absorption of the drugs that are known or suspected of having poor bioavailability. It is believed that such increase can rise from one or all of the following mechanisms:

1. reducing the thickness and/or the viscosity of the mucus layer which is present adjacent to the gastrointestinal mucosa;
2. alteration of the tight junctions between cells, thus promoting absorption through the paracellular route;
3. inducing a change in the cell membrane structure, thus promoting transcellular absorption;
4. increasing the hydrophobic environment within the cellular membrane.

The present dosage forms include an amount of effervescent agent effective to aid in penetration of the drug in the gastrointestinal tract. The amount of effervescent employed must not merely permit rapid dispersion of the medicament in the gastrointestinal tract, but must aid in penetration of the drug across the gastrointestinal mucosa. The formulations of the present invention may be distinguished from other effervescent formulation that are enteric coated on the basis of the amount of effervescent material that they contain. Prior formulations contain approximately half to a quarter as much bicarbonate as drug on a weight basis (together with a proportionate amount of acid). In these cases, the small amount of effervescent couple serves only to rapidly disintegrate the tablet.

The dosage forms of the present invention should preferably contain at least twice as much sodium bicarbonate (or an equivalent amount of other base) as drug (on a weight basis) together with the proportionate amount of an appropriate acid for generating the effervescent reaction. More preferably the present dosage forms should contain at least three times as much sodium bicarbonate as drug (on a weight basis) together with the proportionate amount of an appropriate acid. These high concentrations of effervescent couple are needed to generate effervescence in sufficient amounts to promote permeability and absorption of the drug.

Preferably, the effervescent is provided in an amount of between about 5% and about 95% by weight, based on the weight of the finished tablet, and more preferably in an amount of between about 30% to about 60%. However, the amount of effervescent agent must be optimized for each specific drug.

The term "effervescent penetration enhancer" includes compounds which evolve gas. The preferred effervescent penetration enhancers evolve gas by means of a chemical reaction which takes place upon exposure of the effervescent penetration enhancer to water and other fluids. Such water-activated materials must be kept in a generally anhydrous state and

with little or no absorbed moisture or in a stable hydrated form, since exposure to water will prematurely disintegrate the tablet. The acid sources may be any which are safe for human consumption and may generally include food acids, acid and hydrite antacids such as, for example, citric, tartaric, malic, fumaric, adipic, and succinic. Carbonate sources include dry solid carbonate and bicarbonate salt such as, preferably, sodium bicarbonate, sodium carbonate, potassium bicarbonate and potassium carbonate, magnesium carbonate and the like.

The effervescent penetration enhancers of the present invention is not limited to those which are based upon a reaction which forms carbon dioxide. Reactants which evolve oxygen or other gases and which are safe for human consumption are also considered within the scope of the present invention.

The present dosage forms may also include in amounts additional to that required for effervescence a pH adjusting substance. For drugs that are weakly acidic or weakly basic, the pH of the aqueous environment can influence the relative concentrations of the ionized and the unionized forms of the drug present in solution, according to the Henderson-Hasselbach equation. The pH of solutions in which an effervescent couple with equimolar amounts of base and acid has dissolved is slightly acidic due to the evolution of CO_2 . While it is impractical and may not be desirable to change the pH of the contents of the small intestine, it is, nevertheless, possible to alter the pH of the local environment (intestinal contents in immediate contact with the tablet and any drug that may have dissolved from it). This is achieved by incorporating in the tablet certain pH adjusting substances. Thus, the relative proportions of the ionized and unionized forms of the drug may be controlled.

In this way the system can be optimized for each specific drug under consideration: if the drug is known, or suspected, to be absorbed through the cell membrane (transcellular absorption), it would be most appropriate to alter the pH of the local environment to a level that favors the unionized form of the drug. Conversely, if the ionized form is more readily dissolved the local environment should favor ionization. Thus, for fentanyl, as a nonlimiting example, the pH is adjusted to neutral (or slightly higher) since the pK_a is 7.3. At this pH, the aqueous solubility of this poorly water-soluble drug is not compromised unduly, yet allowing a sufficient concentration of the drug to be present in the unionized form. This facilitates the permeation enhancement brought about by effervescence. In the case of prochlorperazine ($\text{pK}_a=8.1$), a slightly higher pH is required.

Suitable pH adjusting substance for use in the present invention include any weak acid or weak base (in amounts additional to that required for effervescence) or, preferably, any buffer system that is not harmful to the gastrointestinal mucosa. These include, but are not limited to, any of the acids or bases previously mentioned as the effervescent components, sodium carbonate, potassium carbonate, potassium carbonate, disodium hydrogen phosphate, sodium dihydrogen phosphate, and the equivalent potassium salts.

The active agents suitable for use in the present invention preferably includes any drug that displays poor bioavailability, slow absorption or long t_{\max} .

These active ingredients include small molecule drugs, nutritional supplements (such as vitamins and minerals), proteins and peptides and other substances of biological origin. Examples of such drugs include, but are not limited to, the following:

Drug	Bioavailability (%)
Acyclovir	15-30
Auranofin	15-25
Bretylium	23 \pm 9
Cyclosporine	23 \pm 7
Cytarabine	20
Doxepin	27 \pm 10
Doxorubicin	5
Hydralazine	16-35
Ketamine	20 \pm 7
Labetalol	18 \pm 5
Mercaptopurine	12 \pm 7
Methyldopa	25 \pm 16
Nalbuphine	25 \pm 16
Naloxone	2
Pentoxifylline	19 \pm 13
Pyridostigmine	14 \pm 3
Terbutaline	14 \pm 2
Verapamil	22 \pm 8
Riboflavin	11
Atenolol	50

Pharmaceutical ingredients suitable for use in the present dosage forms may include, without limitation, analgesics, anti-inflammatories, antipyretics, antibiotics, antimicrobials, laxatives, anorexics, antihistamines, antiasthmatics, antidiuretics, antifatulents, antimigraine agents, antispasmodics, sedatives, antihyperactives, antihypertensives, tranquilizers, decongestants, beta blockers; peptides, proteins, oligonucleotides and other substances of biological origin, and combinations thereof. Also encompassed by the terms "active ingredient(s)", "pharmaceutical ingredient(s)" and "active agents" are the drugs and pharmaceutically active ingredients described in Mantelle, U.S. Pat. No. 5,234,957, in columns 18 through 21. That text of Mantelle is hereby incorporated by reference. Alternatively or additionally, the active ingredient can include drugs and other pharmaceutical ingredients, vitamins, minerals and dietary supplements as the same are defined in U.S. Pat. No. 5,178,878, the disclosure of which is also incorporated by reference herein.

The dosage forms preferably contain materials that aid in releasing the drug in a specific section of the gastrointestinal tract thus promoting site-specific delivery. There are various mechanisms by which such materials promote site-specific delivery and this invention is not limited to any one mechanism. For example, the material may be metabolized by enzymes present in a specific part of the gastrointestinal tract, thus releasing the drug in that section.

The materials used to promote site-specific absorption may preferably be included

as coatings and/or as matrix materials. If a coating is used, it may be applied to the entire dosage form or to the individual particles of which it consists. Coating materials may be used to prevent the release of the active agent before the dosage form reaches the site of more efficient absorption.

The coating can also be used in conjunction with an effervescence to cause the effervescence to occur at specific areas of the gastrointestinal tract. Nonlimiting examples or coatings used in the present invention include: cellulose derivatives including cellulose acetate phthalate (CAP); shellac and certain materials sold under the trademark Eudragit.TM. (various grades may be used in specific combinations). Hydroxypropylmethyl cellulose phthallate in a grade that dissolves at pH 5 is the preferred coating material.

Precoating materials may also be used in the present invention. Nonlimiting examples include cellulose derivatives such as methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose or combinations and certain materials sold under the trademark Eudragit.TM. (various grades which may be combined). Hydroxypropylmethyl cellulose phthallate in a grade that dissolves at pH 5 is the preferred coating material.

Other materials may be used to aid in site specific delivery, and include, for example, sugars, polysaccharides, starches, polymers, etc. These compounds may be included as coatings or as matrix materials and aid in releasing the drug in specific sections of the gastrointestinal tract, thus promoting site-specific delivery.

Other ingredients or techniques may preferably be used with the present dosage forms to enhance the absorption of the pharmaceutical ingredient, to improve the disintegration profile, and/or to improve the organoleptic properties of the material and the like. These include, but are not limited to, the use of additional chemical penetration enhancers, which are referred to herein as noneffervescent penetration enhancers; absorption of the drug onto fine particles to promote absorption by specialized cells within the gastrointestinal tract (such as the M cells of Peyer's patches); ion pairing or complexation; and the use of lipid and/or surfactant drug carriers. The selected enhancement technique is preferably related to the route of drug absorption, i.e., paracellular or transcellular.

A bioadhesive polymer may preferably be included in the drug delivery device to increase the contact time between the dosage form and the mucosa of the most efficiently absorbing section of the gastrointestinal tract. See Jonathan D. Eichman, "Mechanistic Studies on Effervescent-Induced Permeability Enhancement," University of Wisconsin-Madison (1997), hereby incorporated by reference. Nonlimiting examples of known bioadhesives used in the present invention include: carbopol (various grades), sodium carboxy methylcellulose, methylcellulose, polycarbophil (Noveon AA-1), hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium alginate, and sodium hyaluronate.

Disintegration agents may also be employed to aid in dispersion of the drug in

the gastrointestinal tract. Disintegration agents include any pharmaceutically acceptable effervescent agent. In addition to the effervescence-producing disintegration agents, a dosage form according to the present invention may include suitable noneffervescent disintegration agents. Nonlimiting examples of disintegration agents include: microcrystalline cellulose, croscarmellose sodium, crospovidone, starches and modified starches.

Apart from the effervescent material within the tablet, some additional effervescent components or, alternatively, only sodium bicarbonate (or other alkaline substance) may be present in the coating around the dosage form. The purpose of the latter effervescent/alkaline material is to react within the stomach contents and promote faster stomach emptying.

The drug delivery device may be in the form of a tablet, granules, pellets or other multiparticulates, capsules that can contain the drug in the form of minitabets, beads, or a powder, or any other suitable dosage form.

If tablets are used, they may be matrix tablets; layered tablets in which the various components are separated in different layers to optimize their benefits; or other specialized forms of tablets, including nonconventional shapes and geometric arrangements. One example of a nonconventional shape is a flat-faced tablet with a biconcave central zone, as depicted in FIG. 1. The outer, thicker part of the tablet may contain the mucoadhesive material while the inner, thinner segment may contain the drug and effervescent components. This arrangement allows drug release to a segment of the gastrointestinal mucosa in close proximity to the point at which the tablet is attached to the mucosa.

The drug and/or the effervescent material could be present in a sustained release matrix. The whole tablet may consist of this matrix or the matrix may be confined to one, or more, layers of a multilayered tablet. FIG. 2 depicts a multilayered tablet with a central layer containing the drug and optional effervescent material; and two mucoadhesive layers. The tablet would adhere to the mucosa irrespective of its spatial orientation within the intestine.

FIGS. 3 and 4 depict the effervescent layer external to the mucoadhesive layer of each dosage form. FIG. 3 depicts a multilayered tablet in which a central core is completely surrounded by each subsequent layer. Such a tablet may be prepared by a compression coating technique. A similar physical arrangement of layers can also be achieved in a spheroid or pellet which may be prepared by extrusion and spheronization, layering, coating or any combination of these techniques. (See FIG. 4.) The effervescence will cause a thinning of the mucus layer from the gastrointestinal segment, thus facilitating adhesive of the dosage form to the cellular surface rather than to the mucus layer. This arrangement promotes better absorption of the drug.

Tablets can be manufactured by wet granulation, dry granulation, direct compression or any other tablet manufacturing technique. The tablet may be a layered tablet consisting of a layer of the active ingredients set forth above in layers of diverse compositions. In accordance with the present invention,

the tablet size is preferably up to about 3/4". In accordance with the present invention, the multiparticulate size is preferably up to about 3 mm. In accordance with the present invention, the tablet hardness is preferably between about 5N and 100N.

Excipient fillers can be used in connection with the present invention to facilitate tableting. Nonlimiting examples of fillers include: mannitol, dextrose, lactose, sucrose, and calcium carbonate.

Pellets or other multiparticulates may be manufactured by granulation, layering techniques, extrusion and spheronization or other pellet manufacturing methods. The multiparticulates are then coated with an enteric coating material as described for tablets. The coating is preferably done in a fluid bed coater. The preferred, but nonlimiting, coating material is hydroxypropylmethyl cellulose in a grade that dissolves at pH 5. The multiparticulates are then packed into capsules.

The granules may be made by a wet granulation process or a dry granulation process. When wet granulation is used, isopropyl alcohol, ethyl alcohol or other nonaqueous granulating agent is used. Low moisture content grades of these organic solvents are used.

Dry granulation may be achieved through slugging or chilsonation. Layering may be done in a fluid bed apparatus or coating pan. Nonaqueous binders are used to aid the adherence of the added material (drug, effervescent penetration enhancer and excipients) to the starting material. Nonlimiting examples of the starting material or cores are nonpareils (sucrose) or microcrystalline cellulose seeds.

The preferred technique for the manufacture of multiparticulates is extrusion and spheronization. The beads contain the drug, effervescent couple (as previously described), a fine particle diluent which also aids in the formation of the beads (examples are lactose and mannitol) and a spheronization aid such as microcrystalline cellulose. The preferred grade of the latter is Avicel RC 591 which contains sodium carboxymethyl cellulose as an additional ingredient. For this formulation, a nonaqueous solvent is used. Nonlimiting examples of nonaqueous solvents are isopropanol and ethanol. Low moisture content grades are used.

The alternate (and preferred) formulation is to manufacture two populations of beads, one containing the acid component and the other the alkaline component of the effervescent couple. Each population of beads contains similar drug concentrations and can be manufactured using water. Care should be taken to ensure that each population of beads has a similar size range and a similar density. Equal densities may be achieved by the incorporation of a nontoxic material of high density to the population of beads that would, otherwise, have had a lower density. A nonlimiting example of such a material is barium sulfate. Equivalence of size and density facilitates the achievement of similar emptying rates of the beads from the stomach once the dosage forms are consumed by the subject. When the beads

come into contact with the intestinal fluids, the coating dissolves and the close proximity of the beads to each other allows the effervescent reaction to occur in situ.

The coating applied to the dosage forms of the present invention must be performed with precision to avoid pinhole faults since water penetration through such faults leads to rapid and premature disintegration of the tablet. Such coating can be performed by one skilled in the art who, additionally, takes precautions to limit abrasion and chipping of the partially formed coat during the coating process. A fluid bed coater, pan coater or other coating apparatus may preferably be used.

The invention will be further described by reference to the following detailed examples. These examples are provided for the purposes of illustration only, and are not intended to be limiting unless otherwise specified.

INGREDIENTS	mg/TABLET
Riboflavin, USP	5
Silicified Microcrystalline Cellulose	19.7
Sodium Bicarbonate	18.2
Citric Acid, Anhydrous	13
Crospovidone	3
Magnesium Stearate	0.9
Colloidal Silicon Dioxide	0.5
TOTAL	60

The tablets were compressed to a hardness of 50 N using 3/16 inch concave punches. The tablets had a friability of less than 0.25%. Coating solution was prepared according to the following formula:

INGREDIENTS	WEIGHT (gm)
Hydroxypropylmethyl cellulose	418.5
phthallate	
Triethylcitrate	31.5
Ethanol	2025.0
Acetone	2025.0
TOTAL	4500.0

Using a fluidized bed coater, the tablets were coated to a 15% weight gain. Care was taken to fluidize the bed sufficiently so that agglomeration of the tablets did not occur during coating but excessive movement was avoided to minimize chipping of the tablets or abrasion of the coating material.

INGREDIENTS	mg/PER TABLET
Atenolol	7.143
Sodium bicarbonate	15.000
Citric acid	10.714
Silicified microcrystalline cellulose	26.043
Magnesium stearate	0.900
Silicon dioxide	0.200
TOTAL	60.000

The tablets were compressed using 3/16 inch concave punches to a hardness of 40 N. The tablets were coated with hydroxypropylmethyl cellulose phthalate solution as described above to a weight gain of 15%. Seven tablets were packed into a size 0 elongated capsule to form the final dosage form.

INGREDIENTS	mg PER CAPSULE
Atenolol	25
Sodium bicarbonate	150
Lactose	37
Avicel RC 591	38
Water	Qs
TOTAL	250

The dry powders were blended together. Water was slowly added with mixing until a wet mass that was plastic (but not tacky) was formed. The wet mass was passed through an extruder. The extruded material was spheronized for 3 minutes. The beads that were formed were air dried for one hour and then dried in an oven at 35°C. overnight. The beads were sieved to remove large particles and fines.

INGREDIENTS	mg PER CAPSULE
Atenolol	25
Citric acid	107
Lactose	80
Avicel RC 591	38
Water	Qs
TOTAL	250

Population 2 was made in a similar fashion to population 1. Each population of beads was separately coated to a 20% weight gain in a fluidized bed coater using the previously described coating solution. Two hundred and fifty milligrams of each population of beads was filled into size 0 elongated capsules and this formed the final dosage form.

Various modifications of the invention described herein will become apparent to those skilled in the art. Such modifications are intended to fall within the scope of the appending claims.

Claim 1 of 13 Claims

What is claimed is:

1. A dosage form for delivery of a therapeutically effective amount of a drug to a target area in the gastrointestinal tract of a mammal; comprising:

(a) a therapeutically effective amount of a drug;

(b) at least one effervescent penetration enhancer; wherein said at least one effervescent penetration enhancer is present in an amount sufficient to increase the penetration of said drug across said target area of said gastrointestinal tract to permit delivery of a therapeutically effective amount of said drug; and

(c) an enteric coating maintained over said drug and said at least one effervescent penetration enhancer; wherein said enteric coating prevents the release of said drug and said at least one effervescent penetration enhancer until a time at which said dosage form reaches said target area in said gastrointestinal tract.

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Edited by Magda A. El-Nokaly and Helena A. Soini

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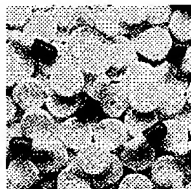
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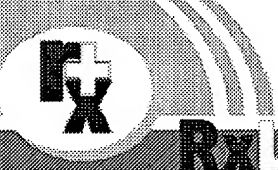

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Isosorbide mononitrate is a white, crystalline, odorless compound which is stable in air and in solution, has a melting point of about 90°C, and an optical rotation of +144° (2% in water, 20°C).

Isosorbide mononitrate is freely soluble in water, ethanol, methanol, chloroform, ethyl acetate, and dichloromethane.

Each Ismo tablet contains 20 mg of isosorbide mononitrate. The inactive ingredients in each tablet are D&C yellow 10 aluminum lake, FD&C yellow 6 aluminum lake, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 20, povidone, silicon dioxide, sodium starch glycolate, titanium dioxide and hydroxypropyl cellulose.

Imdur tablets contain 30 mg, 60 mg, or 120 mg of isosorbide mononitrate in an extended-release formulation. The inactive ingredients are aluminum silicate, colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide,

hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, paraffin wax, polyethylene glycol, titanium dioxide, and trace amounts of ethanol.

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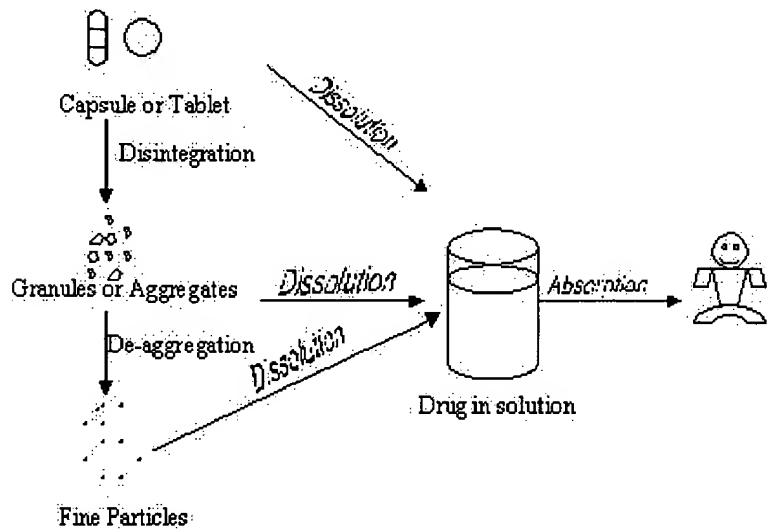
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TABLET & ITS DISSETEGRATION

Following oral administration, a tablet or other solid drug disintegrates into granules, and these granules de-aggregate in turn into fine particles. Disintegration, de-aggregation, and dissolution may occur simultaneously with the release of a drug from its delivery form. The effectiveness of a tablet in releasing its drug for systemic absorption depends on the rate of disintegration of the dosage forms and de-aggregation of the granules.



Tablet Types:

Depending on the mode of use, tablets can be divided into the following categories:

1. Tablets that are swallowed whole
2. *Effervescent tablets* that need to be dissolved in water prior to administration
3. *Chewable tablets* are used where buccal absorption is desired. For example, **antacid** tablets should be chewed to obtain quick indigestion relief.
4. tablets that dissolve slowly in the mouth, cheek pouch (buccal) or under the tongue (sublingual). Examples are *isoprenaline sulphate* (Bronchodilator) and *glyceryl trinitrate* (vasodilator) tablets.
5. Controlled release tablets → improved patient compliance, reduced side effects. For example, *aspirin* has been shown to produce less gastric bleeding when formulated as a sustained release formulation than conventional tablets. *Aminophylline* has a narrow therapeutic blood level range.
6. Coated Tablets (*to prevent decomposition or to minimize the unpleasant taste of certain drugs*). There are several types of coated tablets: film coated, sugar coated, gelatin coated (gel caps), or enteric coated tablets. Coatings can be applied which are resistant to gastric juices, but readily dissolve in the small intestine. These enteric coatings can protect drugs against decomposition in the acid environment of the stomach.

Essential Properties of Tablets

1. must be uniform in weight, appearance, diameter and drug loading
2. should readily disintegrate in the stomach (if designed to be swallowed whole)
3. must dissolve in the gastric/intestinal fluids before absorption can take place.

Tablet Formulation:

In addition to the bioactive drug, the following materials are added to make the powder system compatible with tablet formulation by compression or granulation methods:

1. *Diluents*- bulking agents added to the active ingredient. Commonly used diluents are lactose, dicalcium phosphate, starches, **microcrystalline cellulose** (MCC), dextrose, sucrose, mannitol, sodium chloride. *Dicalcium phosphate* absorbs less moisture than lactose and is therefore used with hygroscopic drugs such as *pethidine hydrochloride*.
2. *Adsorbents*- substances capable of holding quantities of fluids in an apparently dry state. Oil soluble drugs or fluid extracts can be mixed with adsorbents and then granulated and compressed into tablets. Examples are fumed silica, **microcrystalline cellulose**, **magnesium** carbonate, kaolin, bentonite.
3. *Moistening agents*- used for wet granulation. Examples: water, industrial methylated spirits, isopropanol
4. *Binding agents (adhesives)*- bind powders together in the wet granulation process. Also help bind granules during compression. Examples are starch, gelatin, polyvinylpyrrolidone, alginic acid derivatives, **cellulose** derivatives, glucose, sucrose. Choice of binders affects the dissolution rate. For example, the tablet formulation of frusemide with PVP has t_{50} of 3.65 min, but with starch mucilage t_{50} of 117 min.
5. *Glidants* are materials, which are added to tablet formulations to improve the flow properties of the granulations. Commonly used glidants are fumed (colloidal) silica, starch and talc.
6. *Lubricants* are required to prevent adherence of the granules to the punch faces and dies. Commonly used lubricants are **magnesium** stearate, talc, stearic acid and derivatives, MCC, PEG,

- paraffin, sodium or **magnesium** lauryl sulfate.
- 7. *Disintegrating Agents* are added to the tablets to promote breakup of the tablets when placed in the aqueous environment. This increases the surface area and encourage rapid release of the drug. Examples include starch, cationic exchange resins, cross-linked polyvinylpyrrolidone, celluloses, modified starches, alginic acid and alginates, **magnesium aluminum silicate**, and sodium carboxymethylcellulose.

Disintegration Test measures the time it takes for a tablet to break down and pass through a standard screen.

Disintegration, Dissolution and Absorption

A solid drug product has to disintegrate into small particles and release the drug before absorption can take place. However, tablets that are intended for chewing or sustained release do not have to undergo disintegration. The various excipients for tablet formulation affect the rates of disintegration, dissolution and absorption. Systemic absorption of most products consists of a succession of rate process, such as

- 1) disintegration of the drug product and subsequent release of drug
- 2) dissolution of the drug in an aqueous environment
- 3) absorption across cell membranes into systemic circulation

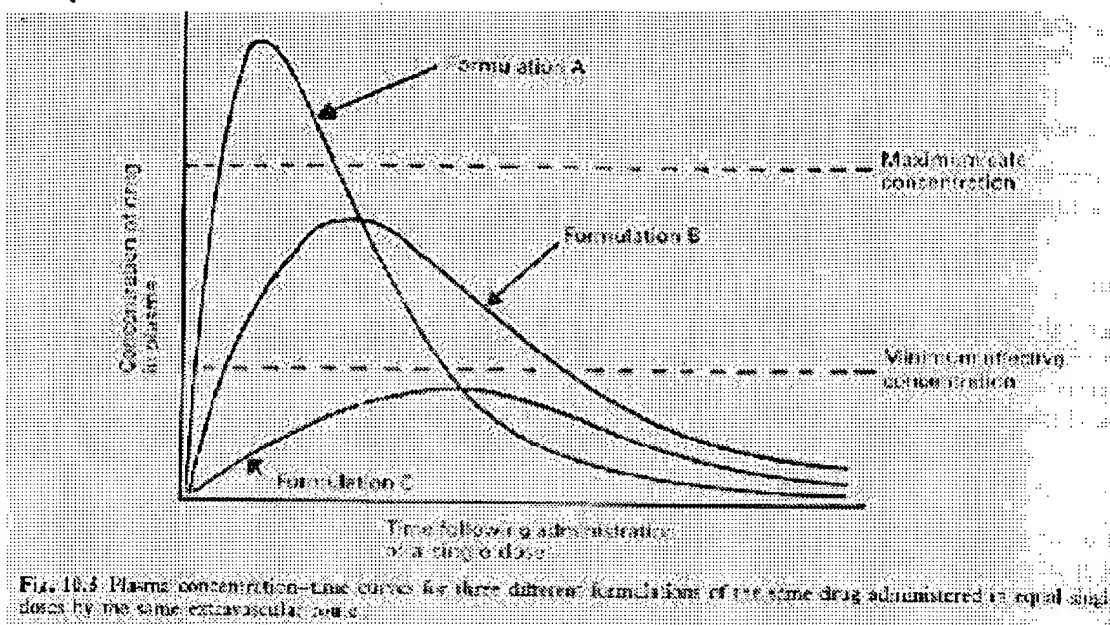
Rate Limiting Step for Disintegration

In the process of tablet disintegration, dissolution and absorption, the rate at which drug reaches the circulatory system is determined by the slowest step in the sequence. Disintegration of a tablet is usually more rapid than drug dissolution and absorption. For the drug that has very poor aqueous solubility, the rate at which the drug dissolves (dissolution) is often the slowest step, and therefore exerts a rate limiting effect on drug bioavailability. In contrast, for the drug that has a high aqueous solubility, the dissolution rate is rapid and the rate at which the drug crosses or permeates cell membranes is the slowest or rate-limiting step.

Oral Bioavailability

Bioavailability is the measurement of the rate and extent of active drug that reaches the systemic circulation. It is thus concerned with the quantity and rate at which the intact form of a particular drug appears in the systemic circulation following administration of that drug. It plays an important role in determining whether a therapeutically active concentration is achieved at the site(s) of action of the drug. According to the definition of bioavailability, an administered dose of a particular drug in an oral dosage form will be 100% bioavailable only if the drug is completely released from the dosage form into solution in the gastrointestinal fluids. The released drug must be completely stable in solution in the gastrointestinal fluids and all of the drug must pass through the gastrointestinal barrier into the mesenteric circulation without being metabolized. Finally, all of the absorbed drug must pass into the systemic circulation without being metabolized on passing through the liver.

Use of Plasma Concentration-Time Curves In Bioavailability Studies



Absolute and Relative Bioavailability

The absolute bioavailability of a given drug from a dosage form is the fraction (or percentage) of the administered dose, which is absorbed intact into the systemic circulation. The absolute bioavailability of a given drug may be calculated by comparing the total areas under the plasma concentration-time curves obtained following the administration of equivalent doses of the drug via an adsorption site and via the intravenous route to the same subject on different occasions. That is,

$$\text{Absolute bioavailability} = (AUC_T)_{\text{abs}} / (AUC_T)_{i.v.}$$

In the case of drugs, which cannot be administered intravenously, the relative bioavailability is determined. The relative bioavailability is a measure of the fraction (or percentage) of a given drug that is absorbed intact into the systemic circulation from a "test" dosage form relative to a standard (or clinically proven) dosage form. For equivalent doses of administered drug,

$$\text{Relative bioavailability} = (AUC_T)_{\text{test}} / (AUC_T)_{\text{standard}}$$

Factors Affecting Oral Bioavailability:

- Rate of drug release from dosage form
- Stability and dissolution rate of drug in gastrointestinal fluids
- Permeability through gastrointestinal barrier
- Drug stability in hepatic portal circulation

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Learning Aids

Updated July 28, 2002, gwood@utmem.edu

The purpose of this site is to aid the first professional year pharmacy student in mastering the basic concepts of physical pharmacy pertaining to dosage forms. It is solely for the use of students and the course website requires a password to view the information. The listings are for the Fall 2002 semester only. The required text book is Martin's Physical Pharmacy, 4th Edition, Lea and Febiger, Philadelphia.

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TAISHO PHARMACEUTICAL CO., LTD.



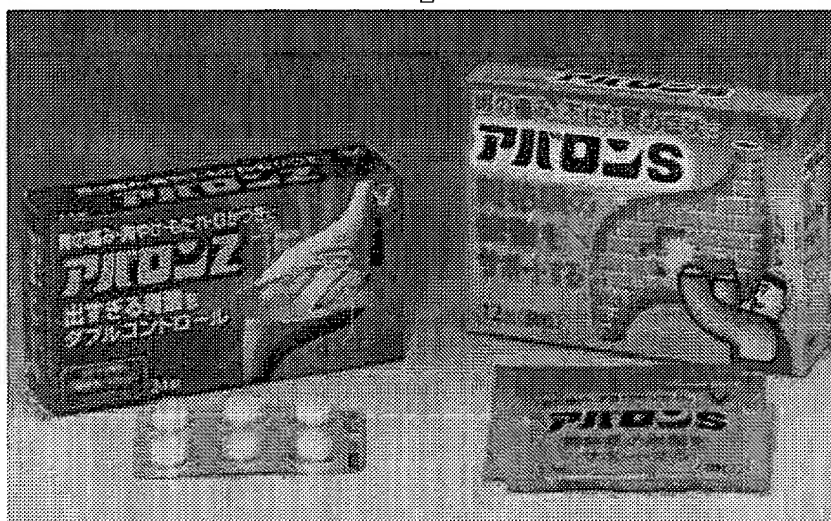
N E W S R E L E A S E



May 30, 2002

Taisho Launches Avalon Z Antacid Medication with Histamine H2 Blocker Ranitidine

□



(left:Avalon Z,right:Avalon S)

Taisho Pharmaceutical Co., Ltd. (President: Akira Uehara) launched sales of Avalon Z, a general purpose stomach medication containing the histamine H2 blocker Ranitidine and ingredients to neutralize gastric acids, on June 3, 2002.

Avalon Z is formulated with the histamine H2 blocker Ranitidine as well as three active ingredients that neutralize gastric acids, including **magnesium** aluminosilicate. The three antacids neutralize excessive acids produced in the stomach, while the H2 blocker controls their secretion. The result is outstanding effectiveness for those suffering from gastric pains.

Taisho Pharmaceutical's Taisho Kanpo Ichoyaku, which was released in 1978, has won strong support from gastric medication customers as a self-medication product with improved functions. In fact, it is now is the leading brand of general gastric medication.

In recent years, more people have been suffering gastric distress, and demand for general purpose stomach medications is diversifying. In response, in 1998, Taisho switched Sofalcone, the gastric mucosa repair agent it had developed, from prescription drug to self medication use and launched Avalon S, a gastric medication that is highly regarded. To build the Avalon brand

into a series of gastric pain medications to meet a wider range of consumer needs, Taisho has now strengthened the line by launching Avalon Z with a histamine H2 blocker.

□ Product features

- ? Contains the histamine H2 blocker Ranitidine hydrochloride
- ? Contains three antacids to neutralize excess gastric acid production

□ Product Overview

Name	Avalon Z											
Suggested retail price	24 pills¥1,480 □ 12 pills¥980 □ 4 pills¥360											
Active Ingredients	Ranitidine hydrochloride		63 mg									
	Magnesium aluminometasilicate		250 mg									
	Magnesium oxide		100 mg									
	Magnesium hydroxide		200 mg									
Indications	For stomach pain, heartburn, indigestion, nausea											
Dosage	When experiencing stomach pain, heartburn, indigestion, or nausea, take a single dose, as defined below, with water or warm water.											
	<table><tr><td>Age</td><td colspan="2">Adult (15-79)</td></tr><tr><td>Dosage</td><td colspan="2">2 tablets</td></tr><tr><td>Frequency</td><td colspan="2">No to exceed two doses a day</td></tr></table>			Age	Adult (15-79)		Dosage	2 tablets		Frequency	No to exceed two doses a day	
	Age	Adult (15-79)										
	Dosage	2 tablets										
	Frequency	No to exceed two doses a day										
	<table><tr><td>Age</td><td>Child (under 15)</td><td>Elderly (80 or above)</td></tr><tr><td>Dosage</td><td colspan="2" rowspan="2">Do not use</td></tr><tr><td>Frequency</td></tr></table>			Age	Child (under 15)	Elderly (80 or above)	Dosage	Do not use		Frequency		
Age	Child (under 15)	Elderly (80 or above)										
Dosage	Do not use											
Frequency												
Release date	June 3, 2002											
Sales objectives for the first year	¥500 million (shipment basis)											

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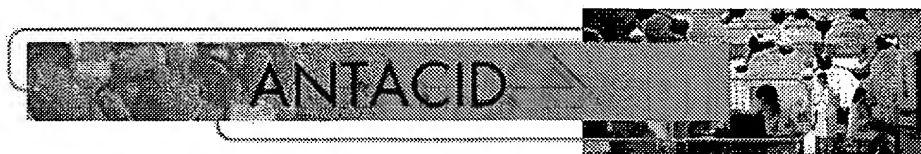
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INON GRANULES

Heartburn, Sour Stomach, Acid Indigestion

Most effectively blends a quick-acting, long-lasting acid control preparation and controls stomach acid for a long time.

Protects injured stomach mucous membrane.

ACTIVE INGREDIENTS: Each packet (1.92g) contains

Aluminum Hydroxide	400mg
Magnesium Carbonate	400mg
Sodium Bicarbonate	700mg

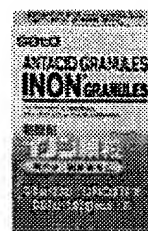
USES:

For the relief of heartburn, sour stomach, acid indigestion, and upset stomach associated with these symptoms.

DIRECTIONS:

Adults and children 12 years and over : Take 1 packet 3 times daily between meals or after meals.

Children under 12 years : Do not take, consult a doctor.



12,30 PACKETS

INON ACE TABLETS

Heartburn, Sour Stomach, Acid Indigestion

Blended with Simethicone, which suppresses gas and relieves bloating in the stomach and intestines.

Suppresses heartburn and other unpleasant symptoms by its combination of two antacids.

ACTIVE INGREDIENTS: Each tablet contains.

Magnesium	
Aluminummetasilicate	200mg
Magnesium Hydroxide	60mg
Simethicone	20mg

USES:

For the relief of heartburn, sour stomach, acid indigestion, and upset stomach associated with these symptoms.

DIRECTIONS:

Adults and children 12 years and over : Take 3 tablets with water 3 times daily between meals and at bedtime. Children under 12 years : Do not take, consult a doctor.

**INON ACE SOLUTION****Heartburn, Sour Stomach, Acid Indigestion**

A drink-type gastrointestinal medicine that quickly relieves such symptoms as heartburn and gastritis.

A most effective blend of antacids.

ACTIVE INGREDIENTS: Each bottle (30ml) contains

Magnesium Aluminosilicate	900mg .
Magnesium Hydroxide	250mg

USES:

relieves these symptoms.

-heartburn -sour stomach -acid indigestion

DIRECTIONS:

Adults and children 12 years and over : Take 1 bottle(30ml) at a times 2 times daily, between meals.

Children under 12 years : Ask a doctor.



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Doxycycline

DESCRIPTION
BRAND

CLINICAL
PHARMACOLOGY

INDICATIONS
and DOSAGE

SIDE EFFECTS
DRUG INTERACTIONS

WARNINGS &
PRECAUTIONS

OVERDOSAGE
CONTRAINDICATIONS

PATIENT
INFORMATION

DESCRIPTION

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Doxycycline is a broad-spectrum **antibiotic** synthetically derived from oxytetracycline and is available as **doxycycline** monohydrate; doxycycline hyclate; **doxycycline hydrochloride** hemiethanolate hemihydrate; and doxycycline calcium for **oral** administration. It is also available as **doxycycline** hyclate for **intravenous** use as well as coated hyclate pellets.

The molecular **formula** of **doxycycline** monohydrate is $C_{22}H_{24}N_2O_8 \cdot H_2O$ and a molecular **weight** of 462.46. The **chemical** designation for doxycycline is 4-(Dimethylamino)-1, 4, 4a, 5, 5a, 6, 11, 12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1, 11-dioxo-2-naphthacene-carboxamide monohydrate. The molecular **formula** for doxycycline **hydrochloride** hemiethanolate hemihydrate is $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_6O \cdot H_2O$ and the molecular **weight** is 1025.89.

Doxycycline is a light-yellow crystalline powder. Doxycycline hyclate is **soluble** in water, while **doxycycline** monohydrate is very slightly **soluble** in water.

Doxycycline has a high **degree** of **lipoid solubility** and a low affinity for **calcium** binding. It is highly **stable** in **normal human** serum. Doxycycline will not degrade into an epianhydro form.

Inert ingredients in the **syrup** formulation are: apple flavor; butylparaben; calcium chloride; carmine; glycerin; hydrochloric acid; **magnesium aluminum silicate; povidone; propylene glycol; propylparaben; raspberry flavor; simethicone emulsion; sodium hydroxide; sodium metabisulfite; sorbitol solution; water.**

Inert ingredients in the capsule formulations are: hard gelatin capsules

Inert ingredients in the capsule formulations are: hard gelatin capsules (which may contain Blue 1 and other inert ingredients); magnesium stearate; microcrystalline cellulose; sodium lauryl sulfate

Inert ingredients for the oral suspension formulation are: carboxymethylcellulose sodium; Blue 1; methylparaben; microcrystalline cellulose; propylparaben; raspberry flavor; Red 28; simethicone emulsion; sucrose.

Inert ingredients for the tablet formulation are: ethylcellulose; hydroxypropyl methylcellulose; magnesium stearate; microcrystalline cellulose; propylene glycol; sodium lauryl sulfate; talc; titanium dioxide; Yellow 6 Lake.

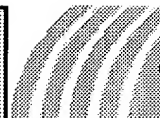
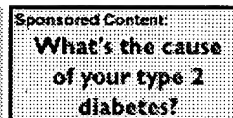
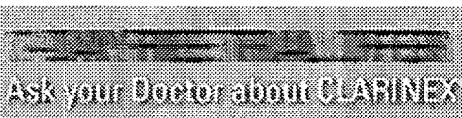
Inert ingredients for the coated pellets are lactose, NF; microcrystalline cellulose, NF; povidone, USP. Each shell and/or band contains FD and C blue No. 1; FD and C yellow No. 6, D and C yellow No. 10; gelatin NF; silicon dioxide; sodium laurel sulfate, NF; titanium dioxide, USP.

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Highlighted Publications can be read using 

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Contact **Penwest Pharmaceuticals Co.**

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S J Edge